2011-12-01

The Effect of Combined Moderate-Intensity Training on Immune Functioning, Metabolic Variables, and Quality of Life in HIV-infected Individuals Receiving Highly Active Antiretroviral Therapy

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THE EFFECT OF COMBINED MODERATE-INTENSITY TRAINING ON IMMUNE FUNCTIONING, METABOLIC VARIABLES, AND QUALITY OF LIFE IN HIV-INFECTED INDIVIDUALS RECEIVING HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

By

Eduard Tiozzo

A DISSERTATION

Submitted to the Faculty of the University of Miami

in partial fulfillment of the requirements for

degree of Doctor of Philosophy

Coral Gables, Florida

December 2011

UNIVERSITY OF MIAMI

A dissertation submitted in partial fulfillment of
the requirements for the degree of
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The Effect of Combined Moderate-Intensity Training on Immune Functioning, Metabolic Variables, and Quality of Life in HIV-Infected Individuals Receiving Highly Active Antiretroviral Therapy

(December 2011)

Abstract of a dissertation at the University of Miami

Dissertation supervised by Professor Arlette Perry
No. of pages in text (39)

Highly-active antiretroviral therapy (HAART) has improved the prognosis of HIV-infected individuals. Unfortunately it has also been associated with impaired functional capacity and development of metabolic perturbations which increases health risk. This study tested the hypothesis that a combined cardiorespiratory and resistance exercise training (CARET) intervention may result in significant health benefits in HIV-infected individuals receiving HAART. Thirty-seven HIV-infected men and women, predominantly of lower socioeconomic status (SES), were recruited and randomly assigned to: 1) a group of moderate-intensity CARET for three months or 2) a control group receiving no exercise intervention for three months. At baseline and following the intervention, physical characteristics (body weight, body mass index, waist circumference, and blood pressure), physical fitness variables (estimated VO_{2max} and one repetition maximum for upper and lower body), metabolic variables (fasting glucose and serum lipids), immune functioning (CD4+ T Cell count, CD4/CD8 ratio, and HIV RNA viral load), and quality of life (SF-36 Health Survey) were measured. Exercise participants evidenced increases in estimated VO_{2max} (21%, $p < 0.01$), upper body strength (15%, $p < 0.05$), and lower body strength (22%, $p < 0.05$), while showing

reductions in waist circumference (-2%, $p < 0.05$), and fasting glucose (-16%, $p < 0.05$). While the control group showed a significant decrease in CD4+ T cell count (-16%, $p < 0.05$) from baseline, the exercise group maintained a more stable count following training (-3%, $p = 0.39$). Finally, the exercise participants showed self-reported improvements in physical (11%, $p < 0.03$) and mental (10%, $p < 0.02$) quality of life. In conclusion, our study demonstrated that a three-month supervised and moderate intensity CARET program performed three times a week, can result in significant improvements in physical characteristics, physical fitness, metabolic variables, and physical and mental quality of life. Furthermore, the same intervention resulted in more favorable immunological responses following training in HIV-infected individuals of lower SES.

Key words: Highly active antiretroviral therapy, HIV, combined aerobic and resistance exercise training, cardiorespiratory fitness, muscular strength, and immune functioning.

Acknowledgment

I am deeply grateful to my advisor, Professor Arlette Perry, for her endless help and support. Without her guidance and trust my journey to this project and clinical research work would not be possible. I would also like to thank my supervisor, Associate Professor John E. Lewis, for offering me this project. I thank him for his ever-present availability and promptness in answering gazillion emails and phone calls. His constant help and encouragement along the way was invaluable. My special thanks also goes to Asociate Professor Kevin Jacobs for always finding time (and answers) to my questions and for reminding me that the light at the end of the tunnel was never (too) far. I would also like to thank Associate Professor Kent Burnett for being a member of my committee. His kindness and advice were very much appreciated.

My special thanks go to Dr. Allan Rodriguez, Dr. Jayaweera Dushyantha, Kathleen Mercogliano, and to all personal trainers (Miguel Figueroa, Joanna Torrens, Sussana Leonard, Molly Piccione, Andre Abadin, Chad Parvus, and Jared Tannenbaum) for their time and dedication to this project. Furthermore, I could not imagine more enjoyable environment than Complementary and Integrative Medicine at the Department of Psychiatry and Behavioral Science for conducting this project. My gratitude goes to Associate Professors, John E. Lewis and Janet Konefal. Also many thanks to Angelica Melillo, Larry Chen, Donna L. Franklin, and Ronnie D. Kanka for always being helpful.

I would like to thank Maria Paolercio as well as Cathy Ferguson and Mike Whitney for letting me use their departments' laptop.

I would also like to thank all my close friends (Daniel, Pablo, Lori, Gerardo, Olga, Tatjana, Carol, Angela, Sam, Robert, Suzy, Bart, Yi-Tzu, Abby……and all my

Team E. & FLA swim friends) for their constant help and encouragement when days were long and money short.

Lastly, I would like to thank my family for their support. I am greatly indebted to my mother, Neda Tiozzo, for being with me every step of the way. I dedicate this thesis to her.

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LIST OF ABBREVIATIONS

1RM: One repetition maximum

AIDS: Acquired immune deficiency syndrome

BMI: Body mass index

BW: Body weight

CD4+: CD4+ cell count

CON: Control group/participants

DBP: Diastolic blood pressure

EX: Exercise group/participants

FG: Fasting glucose

HC: Hip circumference

HDL-C: High-density lipoprotein cholesterol

HIV: Human immunodeficiency virus

HIV RNA: HIV RNA viral load

HR: Heart rate

LDL-C: Low-density lipoprotein cholesterol

PRE: Baseline or pre-intervention evaluation

POST: Immediately post-intervention evaluation

SBP: Systolic blood pressure

TChol: Total cholesterol

TGs: Triglycerides

VLDL-C: Very-low density lipoprotein cholesterol

WC: Waist circumference

WHR: Waist-hip ratio

Chapter 1

Introduction

The development of highly-active antiretroviral therapy (HAART) has revolutionized the treatment of HIV through inhibition of the growth and replication of HIV and a partial reconstitution of the adaptive immune system. For many people, including children, these drugs achieve suppression of symptoms and extend their lives. It is estimated that since its introduction in 1996, HAART has reduced HIV-associated mortality by two-thirds (Palella, Jr. et al., 1998). In addition, the best case estimate of HAART is that it saves 50-75% of a year of life, for each year of therapy (Mustafa et al., 1999).

Unfortunately, along with its benefits, extensive use of HAART results in some known as well as previously unrecognized adverse reactions that were not detected in initial clinical trials. One of the most common adverse reactions to HAART is *lipodystrophy*; a condition characterized by abnormalities in the body's production, utilization, and distribution of fat. One report estimates that up to 75% of HIV-infected and AIDS patients can develop lipodystrophy after 10-12 months on HAART therapy (Dube & Sattler, 1998). Common symptoms include increased storage of adipose tissue in the abdomen, posterior neck ("buffalo hump"), and breasts. *Lipoatrophy* represents a distinct component of lipodystrophy, and it signifies the loss of subcutaneous fat, primarily in the face and proximal extremities. (Hirsch & Battegay, 2002; Lo, Mulligan, Tai, Algren, & Schambelan, 1998; Miller et al., 1998). All of these morphological changes can further contribute to other metabolic consequences that may include: increased total cholesterol (TChol), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TGs), decreased high-density lipoprotein cholesterol (HDL-C), and

impaired glucose metabolism and insulin resistance. It has been estimated that 20-60% of HIV-infected individuals receiving HAART have glucose and/or lipid abnormalities (Carr et al., 1999). Consequently, the clustering of these multiple metabolic abnormalities represents a growing concern for increased risk of cardiovascular disease (CVD) and diabetes mellitus.

Patients may also experience negative psychological responses to the physically-adverse effects of HAART. These psychological responses may include agitation, confusion, anxiety, nightmares, mania, and depression (Reilly, Holzemer, Henry, Slaughter, & Portillo, 1997; Rosenfeld et al., 1999a). In a survey conducted by the International Association of Physicians in AIDS care, the majority of physicians (83.6%) believe the most common adverse psychological responses to HIV are a direct result of the antiretroviral drugs rather than the disease (Horwath, 2011).

All of these physical and psychological adverse reactions can lead to poor compliance and adherence to treatment, which altogether may increase the development of drug resistance. Approximately 25% of patients stop therapy within the first year of HAART because of adverse reactions (d'Arminio et al., 2000). Although HAART reduces HIV-related mortality, the extension in a patient's lifespan comes at the expense of metabolic disorders, adverse health conditions, and a reduction in the quality of life (QOL).

The U.S. Department of Health and Human Services (2008) recommends that in addition to achieving maximum suppression of symptoms for as long as possible HIV/AIDS treatment should focus on QOL (Ryan, 1995). HIV-infected patients can minimize the side effects of HAART by leading a healthy lifestyle, as adjuvant therapy to

their standard HIV treatments. This includes regular physical activity, a healthy diet, sufficient sleep, and smoking cessation. Since HIV/AIDS affects people of lower socioeconomic status (SES) at a disproportionately higher rate, and due to fewer resources, these individuals are frequently left with limited treatment options (Kass, Munoz, Chen, Zucconi, & Bing, 1994). Thus, interventions that promote healthy lifestyle may be of even greater importance for individuals of low SES.

Previous research has examined the benefits of different forms of therapeutic exercise in HIV-infected individuals with aerobic exercise representing the most widely used type of training. The research suggests that HIV-infected individuals can gain significant physical and physiological benefits from aerobic exercise after 12 weeks of training if performed three times a week at moderate intensity (Terry et al., 2006). More specifically, aerobic exercise is associated with improved body composition, significant increases in maximal oxygen consumption (VO_{2max}) (Terry et al., 2006), and beneficial lipid changes (Thoni et al., 2002). Fatigue, depression, and anxiety are the most commonly experienced symptoms in HIV-infected individuals (Ciccolo, Jowers, & Bartholomew, 2004) and research shows that aerobic exercise training demonstrates significant reductions in these psychological components (Schlenzig, Jager, & Rieder, 1989). Furthermore, one observational study showed that mean daily physical activity level, assessed by wrist actigraphy, is inversely related to HIV viral load (Bopp, Phillips, Fulk, & Hand, 2003).

Most studies examining resistance exercise and HIV symptomatology have focused predominantly on muscular strength and muscular hypertrophy, rather than immune function or QOL. Previous research shows that resistance exercise is associated

with increases in strength and lean body mass (Roubenoff & Wilson, 2001; Yarasheski et al., 2001) in HIV-infected individuals, regardless of wasting syndrome status. In addition to changes in physical status, four months of progressive resistance training have been shown to significantly decrease fasting serum TGs (Yarasheski et al., 2001).

When it comes to combined aerobic and resistance exercise training (CARET), a recent study performed on patients with type 2 diabetes found that CARET is more beneficial in improving hemoglobin A_{1C} levels than either modality alone (Church et al., 2010). This finding further supports the recommendations of the Federal Physical Activity Guidelines (The U.S.Department of Health and Human Services, 2008) suggesting combined aerobic and resistance training to be a more favorable form of training for public and clinical health. Unfortunately, few studies have examined the effect of CARET in HIV-infected individuals, and the limited literature showed that CARET results in significant improvements in both aerobic fitness and peak strength (Fairfield et al., 2001; Hand et al., 2008; Fillipas, Oldmeadow, Bailey, & Cherry, 2006).

Currently, it is estimated that 84% of Americans diagnosed with HIV utilize HAART, and the interaction of HAART and exercise on psychological and physiological well-being of HIV-infected individuals represents a new area of research (Ciccolo et al., 2004). However, due to a limited recruitment pool and the challenges facing clinical exercise intervention trials, many studies targeting therapeutic exercise in HIV-infected individuals result in vital limitations. These limitations include: 1) non-existing control group to account for co-intervention (Yarasheski et al., 2001; Thoni et al., 2002; Robinson, Quinn, & Rimmer, 2007), and 2) small sample size leading to limited interpretation of the results (Roubenoff et al., 2001; Robinson et al., 2007).

The present three-month study examines the effect of CARET on physical status, metabolic variables, immune function, and QOL in HIV-infected individuals receiving HAART. Furthermore, the study is part of six-month intervention intended for a grant submission. The study is unique in three aspects, as it: 1) has a control group to compare standard medical treatment to the same treatment complemented by the exercise intervention, 2) implements CARET as a more promising health-promoting form of training, and 3) examines the effects of CARET on a more comprehensive set of health outcomes in HIV-infected individuals.

Investigators hypothesized that a 12-week, moderate-intensity CARET program would result in significant improvements in physical characteristics, physical fitness variables, and QOL in HIV-infected individuals compared to control. Furthermore, it was hypothesized that the same intervention would produce significant improvements in metabolic variables, including fasting glucose and the serum lipid profile (T-Chol, LDL-C, HDL-C, and TGs), and immune function (CD4+ T cell count, CD4/CD8 ratio, and HIV RNA viral load) in HIV-infected subjects receiving HAART compared to control.

Chapter 2

Methods

Study Design

This was a two-group, randomized controlled trial that examined the effect of a three-month CARET program for HIV-infected individuals receiving HAART. Evaluations occurred at two time points: 1) prior to the start of the exercise intervention (PRE) and 2) during or the week after the last exercise session (POST). The PRE and POST measurements served to evaluate baseline values and the immediate impact of the intervention, respectively.

Subjects

Thirty-seven HIV-infected men and women were recruited from the UM/Jackson Health System and other local infectious disease clinics in Miami-Dade County. Eligibility criteria included: 1) confirmed HIV infection with CD4+ T cell count ≥350 cells/mm^3, 2) men or women ≥18 years of age, 3) stable HAART treatment in which therapy changes were not planned during the intervention, 4) a sedentary lifestyle, i.e. failing to complete 30 minutes of exercise at least three times a week, as defined by American College of Sports Medicine's (ACSM) Guidelines for Exercise Testing and Prescription (2006), and 5) a commitment to three weekly supervised exercise sessions for 12 weeks. Exclusion criteria included: 1) current opportunistic infection(s), 2) pregnancy, 3) use of lipid-lowering, insulin sensitizing, or hypoglycemic drugs, anabolic steroids, and growth hormone, and 4) any other medical condition or situation precluding adherence to and completion of the protocol.

Procedure

All procedures, including assessment and exercise training, were completed at the Medical Wellness Center (MWC) of the University of Miami Miller School of Medicine. After signing the informed consent form, subjects were assigned an identification number and then assisted in completing a demographic data form, the SF-36 Functional Health Survey, the Stanford 7-Day Physical Activity Recall (PAR), and other pertinent health history information. Following successful completion of the forms, subjects were randomized with a number table to either the CARET intervention exercise (EX) group or a non-intervention control (CON) group. The Institutional Review Board for human subjects at the University of Miami approved the study and its procedures.

Exercise Intervention

Subjects in the EX group participated in a 12-week CARET program, consisting of three exercise sessions a week for a total of 36 sessions. All sessions were supervised by investigators and MWC coaches to ensure that every participant received individual attention.

Table 1 shows a schematic of the EX design. The first two weeks represented a phase-in period allowing participants to familiarize themselves with the exercise equipment and acclimate gradually to the exercise protocol. Both weeks contained three endurance sessions consisting of five-minute warm-up and cool-down periods and 10-15 minutes of aerobic exercise utilizing a stationary treadmill or bicycle ergometer at an intensity of 60% of maximal heart rate (HRmax). All endurance sessions were followed immediately by core exercises (back extension and abdominal crunches) consisting of

two to three sets of 15-20 repetitions, and one set of 12 repetitions for ten exercises (leg press, leg extension, leg curl, chest press, lat pull, shoulder press, seated row, triceps press, biceps curl, and chest fly) performed on stacked-weight machines. The initial level for the resistance exercises was set at 60% of one repetition maximum (1RM).

The following ten weeks of the EX included three phases (Step 1, Step 2, and Step 3 respectively), each consisting of three weekly sessions performed every other day and in a different fashion from the first two weeks: 1) the first weekly session resembled the sessions from the phase-in period, 2) the second weekly session stressed aerobic exercise training of 40-50 minutes on a stationary treadmill or bicycle ergometer, followed by core exercises consisting of three to four sets of 20-30 repetitions, and 3) the third weekly session stressed resistance exercise training (2-3 sets of 8-12 repetitions) for the same ten (3 lower and 7 upper body) weight machine exercises performed after a short warm-up (5-10 minutes) on a stationary treadmill or bicycle ergometer.

After the initial 60% of aerobic training intensity and 60% of 1RM resistance training intensity during the phase-in period, intensity was gradually increased to 65% of HRmax and 65% of 1RM in Step 1 (weeks 3-6), to 70% in Step 2 (weeks 7-9) and to 75% in Step 3 (weeks 10-12). In addition, Step 1 consisted of high repetitions (12), followed by lower repetitions in Step 2 and Step 3 (10 and 8 repetitions, respectively). Furthermore, similar to the phase-in period, other phases also allocated the same amount of time to each component (aerobic versus resistance) of the exercise program.

Control Group

During weeks 0-12, the CON group was asked not to participate in any form of exercise. Its participants were telephoned at weeks 4, 8, and 12 to maintain contact and promote their interest in the study as well as to ensure no changes were made in lifestyle behaviors during the study.

Testing and Laboratory Measurements

Study surveys, physical characteristics, physical fitness variables, fasting glucose, serum lipid markers, CD4+ T cell count, CD4/CD8 ratio, HIV-RNA viral load, and QOL were obtained for all subjects at PRE and POST.

Physical Characteristics

Anthropometric measures included *weight, height,* and *waist and hip circumference*. All measures were conducted by the same investigator using standard techniques: 1) weight using a physician's beam digital scale to within 100 g, barefoot and without heavy clothing, 2) height using a height rod measured to within 0.5 cm (SECA 700, CA, USA) and also barefoot, 3) circumferences measured to within 1 mm using a plastic tape. Waist circumference (WAIST) was measured mid-way between the lowest rib and the iliac crest with the subjects standing at the end of gentle expiration, and hips were measured at the greater trochanter level. *Body mass index (BMI)* was calculated as weight in kilograms divided by height in meters squared. Additionally, *systolic blood pressure (SBP) and diastolic blood pressure (DBP)* were measured to the nearest even digit using a random-zero sphygmomanometer (Mabis, IL, USA). Three readings were

made while subjects were seated after a five minute rest period. The average of the second and third reading was used in the analysis.

Physical Fitness Variables

Submaximal testing for *cardiorespiratory fitness* was performed on a treadmill (Lifestyle Fitness 95T, IL, USA) using the Asymptomatic Cardiac Ischemia Pilot (ACIP) protocol (ACSM, 2006). The subjects were warmed up at 2mph, after which time the speed and/or incline were gradually increased until they reached 85% of age predicted HRMax. Heart rate was monitored with chest-band transmitter and wristwatch display (Polar FT2, NY, USA). Each subject's treadmill time, speed, and incline were recorded and estimated VO_{2max} was predicted from the following formula (ACSM's Guidelines for Exercise Testing and Prescription, 2006):

*Estimated VO2max (ml/kg/min) = (mph * 2.68) + (1.8 * 26.82 * mph * grade/ 100) + 3.5.*

This treadmill protocol showed, when compared to Bruce and Cornell protocols, similar oxygen consumption rate and minute ventilation, (10.2 ± 3.1 vs 13.4 ± 4.9, 13.9 ± 4.5, and 15.0 ± 4.2 minutes, respectively; $p < 0.001$) in healthy patients. However, the difference between predicted and observed VO_2 was smallest for the ACIP protocol (37.0 ± 11.0 vs 35.8 ± 13.5 ml/kg/min, $p = 0.008$) and greatest for the Bruce protocol (41.1 ± 11.8 vs 36.7 ± 15.0 ml/ kg/min, $p < 0.001$) among the same participants (Tamesis et al., 1993). Thus, the ACIP protocol was selected for this study.

The protocol for *1RM testing* followed the same ACSM guidelines to determine *maximum strength* progress from a resistance training program, PRE to POST. More specifically, upper and lower body were assessed by chest press and leg press, respectively (Lifestyle Fitness, IL, USA). The subjects warmed up by completing a

maximum of four trials of 10, 8, 6, and 3 repetitions with a rest period up to 3-4 minutes between trials. The initial weight was selected within the subject's perceived capacity (50-70% of 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.

Metabolic Variables

Ten millimeters of venous blood was taken from the antecubital vein between 7:00 and 9:00 AM following an overnight fast of 10-12 hours.

Plasma glucose was measured by the glucose hexokinase method, and plasma levels of *T-Chol* and *TGs* were measured by enzymatic procedures (Allain, Poon, Chan, Richmond, & Fu, 1974). *HDL-C* was measured by selective inhibition (Warnick, Benderson, & Albers, 1982), and *LDL-C* was calculated by Friedwald equation (Friedewald, Levy, & Fredrickson, 1972):

*LDL-C = T-Chol - (HDL-C – 0.20 * TGs)*

VLDL-C levels were calculated as the TGs level divided by five, unless TGs exceeded 400 mg/dl, in which case VLDL-C was measured by enzymatic methods (Vitros 750 Analyzer, Johnson and Johnson, NY, USA).

Immune Function Variables

The number of *CD4+ T lymphocytes* was measured by flow cytometry (BD FACSCount, NJ, USA) using monoclonal antibodies and plasma *HIV-RNA* was measured by the NASBA Nuclisens method (COBAS AmpliScreen, Roche, QC, Canada) with lower limit of detection 20 copies per milliliter (Terry et al., 2006).

Study Surveys

Functional health and well-being were assessed by the *SF-36 Health Survey*. This is the most widely used generic outcome measure of QOL that has been translated into more than 100 languages (Garratt, Schmidt, Mackintosh, & Fitzpatrick, 2002). This instrument contains 36 questions and evaluates eight areas: 1) physical functioning, 2) social functioning, 3) bodily pain, 4) general health perception, 5) vitality, 6) limitations due to emotional problems, 7) limitations due to physical health problems, and 8) mental health. A review of the first 15 published studies on the SF-36 (McHorney, Ware, Jr., & Raczek, 1993) revealed that the median reliability coefficients for each of the eight scales was equal or greater than 0.80 (except for social functioning, Cronbach's $\acute{\alpha} = 0.76$), while also maintaining good validity ($r = 0.40$ or greater).

Physical activity was assessed by the *Stanford 7-day PAR*. This instrument assesses self-reported amount (number of hours) of work related and non-work related physical activity performed at moderate, physically challenging, and very physically challenging activities over the past seven days. High correlations between the self-administered PAR and the interview administered re-call, and between the self-administered PAR and a daily diary of physical activity have been reported ($r = 0.83$, $p < 0.01$, and $r = 0.82$, $p < 0.01$ respectively) (Dishman & Steinhardt, 1988). Furthermore, the Stanford 7-day PAR is effective for detecting changes in energy expenditure ($r = 0.32$, $p < 0.05$), VO_{2max} ($r = 0.33$, $p < 0.05$), HDL-C ($r = 0.31$, $p < 0.05$), and TGs ($r = -0.41$, $p < 0.01$). As such it provides a useful estimate of habitual physical activity for public health research (Blair et al., 1985).

Statistical Analysis

Data were analyzed using SPSS 18 (IBM Inc, IL, USA). 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] x 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.

Chapter 3

Results

The present study was conducted between December, 2011 and August, 2012. Initial enrollment included 18 EX and 19 CON subjects, with 12 EX and 11 CON participants completing both PRE and POST evaluations (Table 2). Fourteen subjects (6 EX and 8 CON) dropped out the study due to lack of interest or financial/family problems. Participants in the EX group attended on average 29.4 (81%) of the supervised exercise sessions.

The EX group (n=12) consisted of six African American, three Non-Hispanic White, and three Hispanic White individuals while the CON group (n=11) consisted of all African American individuals. The difference in proportion of African Americans between groups was significant (Table 2). Both groups were predominantly represented by individuals of lower SES, earning less than $15,000 per year. Finally, the participants in both groups had been diagnosed with HIV for an average of more than 10 years, and all subjects were receiving HAART therapy (Table 3).

Physical Characteristics. SBP was significantly different between groups at baseline and post training (p=0.024 and p=0.027, respectively) with the CON participants' values being higher at baseline and significantly improved post training. (Table 4). A significant difference for Time x Group interaction was found for WAIST with the EX participants' values decreasing while the CON group's values increased from baseline (p=0.01) (Table 4).

Physical Fitness Variables. Repeated measures ANOVAs indicated Significant main effects of Time and Time x Group interactions were found for VO_{2max} (p=0.001 and

p=0.002 respectively) (Figure 1), 1RM chest (p=0.003 and p=0.018 respectively), and 1RM legs (p=0.01 and p=0.03 respectively) with the EX participants' values increasing and the CON participant's values remaining the same from baseline (Figure 2).

Metabolic Variables. A significant Time x Group interaction was found for FG (p = 0.048) with the EX participants' values decreasing and the CON group's values increasing from baseline (Table 5). Repeated measures ANOVAs for the serum lipid profile indicated no main effects for either Time or Time x Group interactions for TChol (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), TChol/HDL-C (p=0.20 and p=0.96), and TGs (p=0.40 and p=0.90) (Table 5).

Immune Function Variables. A significant main effect of Time and the Time x Group interaction were found for CD4+ T cell count (p=0.002 and p=0.03, respectively) (Figure 3) with the EX participants' values remaining stable and the CON participant's values decreasing from baseline. No significant main effect of Time and Time x Group interactions were observed for CD4/CD8 (p=0.60 and p=0.49) and HIV RNA (Figure 3).

Quality of Life. Significant Time x 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 and the CON participants' values worsening from baseline (Table 6).

Chapter 4

Discussion

The present study showed that a three-month CARET program can lead to substantial improvements in WAIST, physical fitness variables, FG, and QOL in HIV-infected individuals of low SES. Furthermore, the same intervention resulted in more favorable immunological responses following training, compared to standard medical care only.

Our trial exhibited a 38% drop-out rate, 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 others higher than 50% (O'Brien, Nixon, Tynan, & Glazier, 2004). Furthermore, our EX participants achieved higher completion rates than that reported for three similar exercise intervention trials (70%, 77%, and 78% respectively) (Roubenoff et al., 2001; Hand et al., 2008; Fairfield et al., 2001) and the same rate (81%) reported by Fillipas et al. (2006).

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 (132.0 vs 118.9mmHg, respectively; Table 4). This difference may be explained by higher rates of hypertension in African Americans (Douglas et al., 2003) and the fact that the CON group was entirely African-American. That same group experienced significant improvements in SBP (-7%) after the intervention. Since no alterations in antihypertensive medications were made during the trial, it is difficult to explain why SBP improvements were found in the CON group. Despite no significant changes in body weight in either group, the EX group experienced a reduction in WAIST while the CON

group increased their WAIST (-2% vs 1%, respectively). Since HIV-infected individuals receiving HAART are at risk for greater visceral fat accumulation which may positively influence WAIST, they represent a population at greater risk for metabolic abnormalities associated with CVD and diabetes. 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 VO_{2max}, an important measure of aerobic capacity related to health and longevity (Manson et al., 1999; Myers et al., 2002). Generally, aerobic fitness declines at approximately 1% per year in healthy individuals beyond the age of 25 (Rosen, Sorkin, Goldberg, Hagberg, & Katzel, 1998) and even more in adults with chronic diseases (Palella, Jr. et al., 1998). More specifically, conditioned HIV individuals may have up to 9% lower VO_{2max} values, compared to age-matched healthy individuals (Johnson et al., 1990). These decrements subsequently translate into lower endurance, quicker fatigue, and reduced independence during daily life activities in sedentary individuals.

Abnormalities specific to reduced aerobic capacity in HIV-infected population include decreased lactate threshold (Stringer, 2000) and reduced peripheral muscle oxygen utilization during exercise. These problems are often related to mitochondrial toxicity (Cade, Fantry, Nabar, Shaw, & Keyser, 2003) caused by NRTIs, the cornerstone of HAART therapy. Low estimated VO_{2max} values were observed in both CON and EX groups at baseline (21.7 ± 5.9 and 21.9 ± 6.5 ml/kg/min, respectively), signifying low functional aerobic capacity in this sample. This impairment is also supported by other studies showing that sedentary HIV-infected individuals have estimated VO_{2max} values

below 30 ml/kg/min (Keyser, Peralta, Cade, Miller, & Anixt, 2000; Prentiss, Power, Balmas, Tzuang, & Israelski, 2004; Stringer, Berezovskaya, O'Brien, Beck, & Casaburi, 1998; Thoni et al., 2002) with values ranging 24-44% below age-predicted norms (Lox, McAuley, & Tucker, 1996; MacArthur, Levine, & Birk, 1993c). However, despite continued HAART therapy in both groups, the EX group was able to achieve a significant 21% improvements in estimated VO_{2max} (4.7 ml/kg/min) while the CON group showed no significant changes (1.4%, 0.4 ml/kg/min).

In contrast to our results, others have found non-significant 9-10% increases in VO_{2max} following a similar combined training protocol after 12 and 16 weeks in HIV-infected individuals (Robinson et al., 2007; Smith et al. 2001). Our results are more closely related to an older study (Rigsby, Dishman, Jackson, Maclean, & Raven, 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 (MacArthur, Levine, & Birk, 1993b), 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 (Seguin & Nelson, 2003). In our trial, the EX compared to CON group achieved a significant 15% improvement in upper body strength (17.9lbs vs. 2.3lbs, respectively; Fig. 2) and a 21% improvement in lower body strength (49.1lbs vs 1.9lbs, respectively). Increased strength in both upper and lower body strength is associated with improved functional capacity, reduced risk of falls, and a lower incidence of hip fractures

in the elderly (Whipple, Wolfson, & Amerman, 1987). Thus, our findings of improved musculoskeletal strength may have significant implications for improved functional independence later in life.

Despite a shorter length of the present study, the strength gains of the current study were similar to those of a 16-week CARET intervention (Robinson et al., 2007) using participants similar in age to our study. Their trial also showed an average 18% (32.4 lbs) 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 (ranges 34-38% and 23-28%, respectively) in 18 HIV-infected individuals. Smaller increases in upper body strength can be attributed to NRTI medications, resulting in peripheral neuropathy and limited ability to recruit motor nerves in the upper body musculature (Fichtenbaum, Clifford, & Powderly, 1995). This physiological limitation, associated with side effects of NRTIs, signifies the importance of performing more upper body training for HIV population in the future.

Regarding metabolic changes, both groups had normal PRE FG levels, but post intervention, demonstrated trends in opposing directions (Table 5). 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 (Terry et al., 2006) in which a 12-week exercise intervention, combined with a diet, did not improve high FG levels in HIV-infected individuals receiving HAART. In our study, HIV-infected individuals did not present with fasting hyperglycemia. Nonetheless they were able to achieve positive changes in FG following a CARET intervention. Similar prevalence of metabolic syndrome (26%) has been reported for both HIV-infected and general

population (de et al., 2008). However, clinical evidence shows that cumulative exposure to certain NNRTIs and PIs can present independent risk factors for the metabolic syndrome and diabetes (Justman et al., 2003; de et al., 2008). Our results suggest that a 12-week CARET intervention can improve the glycemic status in HIV infected patients and reduce the risk of hyperglycemia associated with HAART.

Past research has shown favorable changes on serum lipids after 12 weeks of training in patients with dyslipidemia, not receiving HAART (Halbert et al., 1997). 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 (Table 5). Overall, our findings are in accordance with two other studies performed in HIV-infected individuals receiving HAART. Terry et al. (2006) showed no significant improvements in TGs, T-Chol, and HDL-C after 12 weeks of aerobic exercise, while other investigators (Birk, MacArthur, Lipton, & Levine, 2002) failed to show significant reductions in serum TGs after 12 months of aerobic exercise. In contrast, Thoni et al. (2002), did find significant improvements in T-Chol, TGs, and HDL-C (-23%, -43%, and +6%, respectively) after 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 program was not of sufficient length.

Immunological markers not only give prognostic information on HIV but they are also linked to HIV-related illness and mortality (Hogg et al., 2001). Recent clinical trials have consistently shown no significant improvements in CD4+ T cell count and/or HIV RNA levels after moderate-intensity training (Smith et al., 2001; Terry, Sprinz, &

Ribeiro, 1999). Our findings confirm these observations. However, the EX participants demonstrated a more stable CD4+ T cell count from baseline, -3% (from 693.8 to 672.9 cells • mm^{-3}), while the CON group experienced significant reductions, -16% (from 612.8 to 511.8 cells • mm^{-3}) during the course of the program. Furthermore, the drop in CD+ T cell count was observed in eight (73%) CON individuals compared to only four (33%) EX participants. Although there were no significant increases in CD4+ T cell count as a result of training, the fact that levels remained fairly stable, is a positive finding for the EX group. Favorable results were also found in viral load with only one EX participant (8%) having higher HIV RNA viral load, compared to four CON participants (36%) demonstrating a higher viral load after the program. 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 immunological responses of our intervention. Our trial included people of lower SES facing greater life-stress and 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 HAART era in which a 10-week aerobic exercise program showed an increase of CD4+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 HAART and subsequently improved immunological profile in the EX group. Similar results on social support and enhanced adherence to HAART have already been demonstrated in several previous studies (Bogart, Kelly, Catz, & Sosman, 2000; Berg et al., 2004; van et al., 2005).

In addition to negative physical and physiological changes, HIV-infected patients receiving HAART can also experience psychological responses such as agitation, confusion, anxiety, nightmares, mania, and depression (Rosenfeld et al., 1999b). Our EX participants noted substantial self-reported improvements in both physical and mental quality of life scales (16%, 8.8 points and 9%, 7.5 points respectively) while the CON participants had lower scores on the same scales (-18%, -14 points and -12%, -9.5 points, respectively). This indicates that the EX participants reported improvements in performing daily activities such as bathing, dressing, walking, climbing stairs, and carrying groceries, which are activities captured in the physical quality of life scale. Furthermore, higher mental quality of life 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 CON participants exhibited negative trends in the same number of 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 count (Leserman et al., 1999).

Several limitations should be noted as a result of the study. First, the small sample size, frequently observed in exercise trials in HIV-infected populations (MacArthur, Levine, & Birk, 1993a; Roubenoff et al., 2001; Robinson et al., 2007) represented a major limitation. Difficulties facing this population often include inadequate transportation, poverty and frequent inpatient and/or outpatient treatments that may interfere with the protocol. Second, most subjects 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 post blood draw appointments. Finally, there was no protocol to formally check for compliance to their medications. Based upon daily communication with each individual, we could only speculate that our study participants were adhering to their HAART regimen. However, several participants from both groups did report a singular short gap (3-5 days) in obtaining their medications from a pharmacy, which ultimately may have affected their immunological response.

In conclusion, our results showed that a three-month, supervised, and moderate intensity CARET program performed three times a week, can result in significant improvements in physical characteristics, physical fitness, and metabolic variables related to overall health in HIV-infected individuals. Reductions in WAIST were observed concomitant with increases in aerobic fitness, muscular strength, and FG in exercising participants. In addition to the aforementioned changes EX participants demonstrated more favorable changes in both physical and mental QOL. Furthermore, favorable clinical findings were demonstrated with respect to immunological markers, signifying that patients of lower SES can attain a more positive prognosis with respect to their HIV-related health outcomes.

Given the promising results of our study, future trials should focus more upon longer duration exercise programs for enhancing the general health status of individuals infected with HIV. Finally, it would be relevant to specifically target HIV patients of

lower SES, since they represent individuals with greater susceptibility to disease progression and premature mortality (Cunningham et al., 2005)

Table 1. Timeline for the Combined Aerobic and Resistance Exercise Training (CARET)

Stages	Week	Sessions (wk)	Type of exercise	Duration (min)	Intensity
Phase-in	0-2	3	Aerobic/Core/ Resistance	15-20/5-10/ 15-20	60% of HRmax/1RM
Step 1	3-6	1	Aerobic/Resistance	20-25/ 20-25	65% of HRmax/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 HRmax/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 HRmax/1RM
		1	Aerobic/Core	45-50 /5-10	
		1	Aerobic/Resistance	5-10/45-50	

HRmax: maximum heart rate, 1RM: one repetition maximum

Table 2. Demographics and Socio-Economic Strata of Control and Exercise Groups

Variable	Category	Control Participants (n=11)	Intervention Participants (n=12)
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)

Table 3. Clinical Characteristics and Medications of Control and Exercise Groups

Variable	Category	Control Participants	Intervention Participants
Years	HIV	10.3±8.4 (3, 28)	12.4±7.8 (5, 34)
HAART	NNRTI+NRTI(s)	6 (54.5%)	3 (25%)
	NNRTI(s)+PI	1 (9.1%)	-
	NNRTI+PI(s)+II	-	1 (8.3%)
	NRTI+PI(s)	4 (36.4%)	4 (33.2%)
	NRTI+II	-	2 (16.6%)
	NNRTIs	-	1 (8.3%)
	PIs	-	1 (8.3%)
Diagnosis	Hypertension	4	2
	Depressions	6	7

Values are mean ± standard deviation (minimum, maximum)

HIV: Human immunodeficiency virus, HAART: highly active antiretroviral therapy, NNRTI: non-nucleoside reverse transcriptase inhibitor, NRTI: nucleoside/nucleotide reverse transcriptase inhibitor, PI: protease inhibitor, II: infusion inhibitor

Table 4. Physical Characteristics of Control and Exercise Groups at Baseline and Following the Intervention

Variable	**Control Participants (CON)**		**Intervention Participants (EX)**	
	Pre	*Post*	*Pre*	*Post*
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
WC (in)	39.1 ± 7.1	39.5 ± 7.5	41.2 ± 8.0	40.4 ± 7.7†
HC (in)	43.1 ± 5.1	43.0 ± 5.7	44.8 ± 8.7	44.3 ± 7.8
WHR	0.9 ± 0.08	0.91 ± 0.07	0.92 ± 0.06	0.91 ± 0.06
SBP (mmHg)	132 ± 16	124 ± 17*	119 ± 9†	120 ± 6
DBP (mmHg)	80 ± 10	81 ± 9	81 ± 5	77 ± 11
HR (bpm)	80 ± 12	81 ± 13	79 ± 10	73 ± 9

Values are mean ± standard deviation (minimum, maximum)

BW: body weight, BMI: body mass index, WC: waist circumference, HC: hip circumference, WHR: waist-hip-ratio, SBP: systolic blood pressure, DBP: diastolic \blood pressure, HR: heart rate, CON: control subject, EX: exercise subjects, PRE: baseline evaluation, POST: immediate post-intervention 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 5. Metabolic Variables of Control and Exercise Groups at Baseline and Following the Intervention

Variable	**Control Participants (CON)**		**Intervention Participants (EX)**	
	Pre	*Post*	*Pre*	*Post*
TChol (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
TChol/HDL	3.5 ± 1.1	3.3 ± 1.3	4.3 ± 1.8	4.2 ± 1.6
TGs (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*

Values are mean ± standard deviation (minimum, maximum)

TChol: total cholesterol, LDL-C: low- density lipoprotein cholesterol: HDL-C: high-density lipoprotein cholesterol, VLDL-C: very-low density lipoprotein cholesterol, TGs: triglycerides, FG: fasting glucose, CON: control subject, EX: exercise subjects, PRE: baseline evaluation, POST: immediate post-intervention evaluation

* Significantly different from CON at the same time point ($p<0.05$, ANOVA)

Table 6. The SF-36 Scales of Control and Exercise Groups at Baseline and Following the Intervention

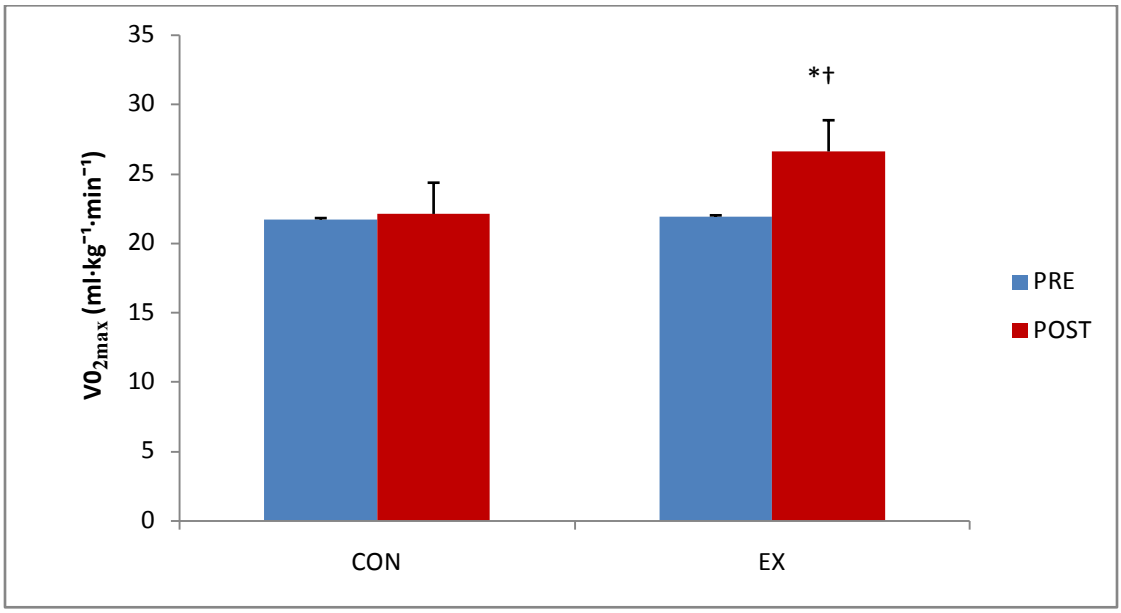
Variable	**Control Participants (CON)**		**Intervention Participants (EX)**	
	Pre	*Post*	*Pre*	*Post*
Physical Functioning	77.2 ± 30.1	63.3 ± 41.6	78.3 ± 31.4	87.1 ± 16.8*
Role - Physical	67.0 ± 25.7	60.8 ± 34.5	73.9 ± 40.7	77.6 ± 23.3
General Health	62.5 ± 24.7	60.3 ± 20.6	75.0 ± 28.1	76.4 ± 24.7
Vitality	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: immediate post-intervention evaluation

* Significantly different from CON at the same time point ($p<0.05$, ANOVA)

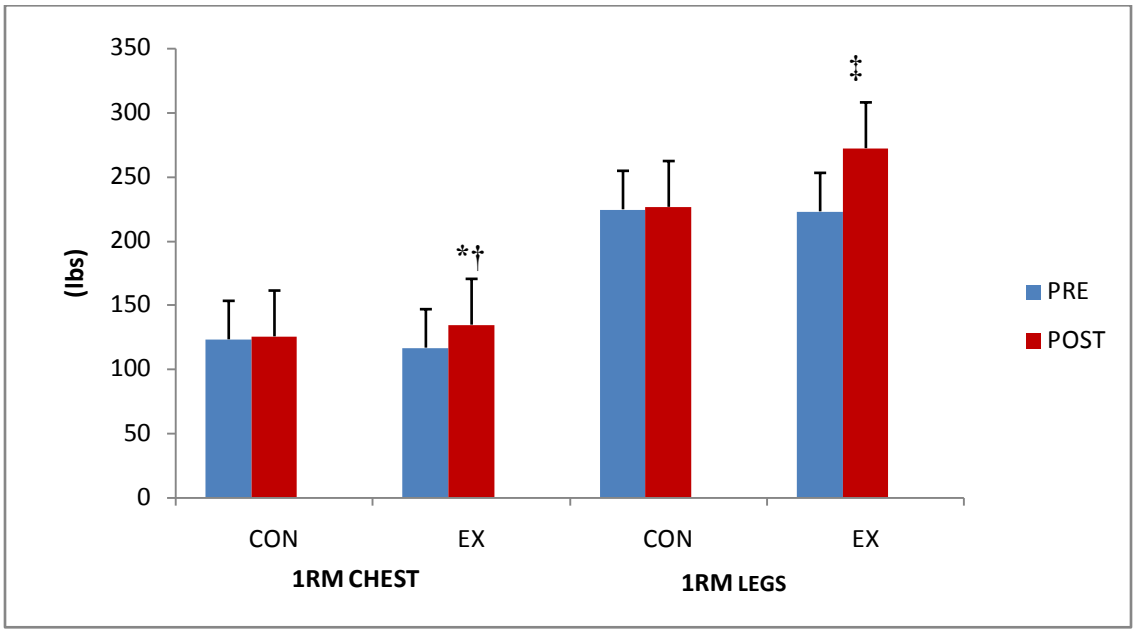
Figure 1. Changes in Maximum Oxygen Consumption (VO_{2max}) in Control and Exercise Groups at Baseline and Following the Intervention



Estimated VO2max: estimated maximal oxygen consumption, CON: control subject, EX: exercise subjects, PRE: baseline evaluation, POST: immediate post-intervention 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)

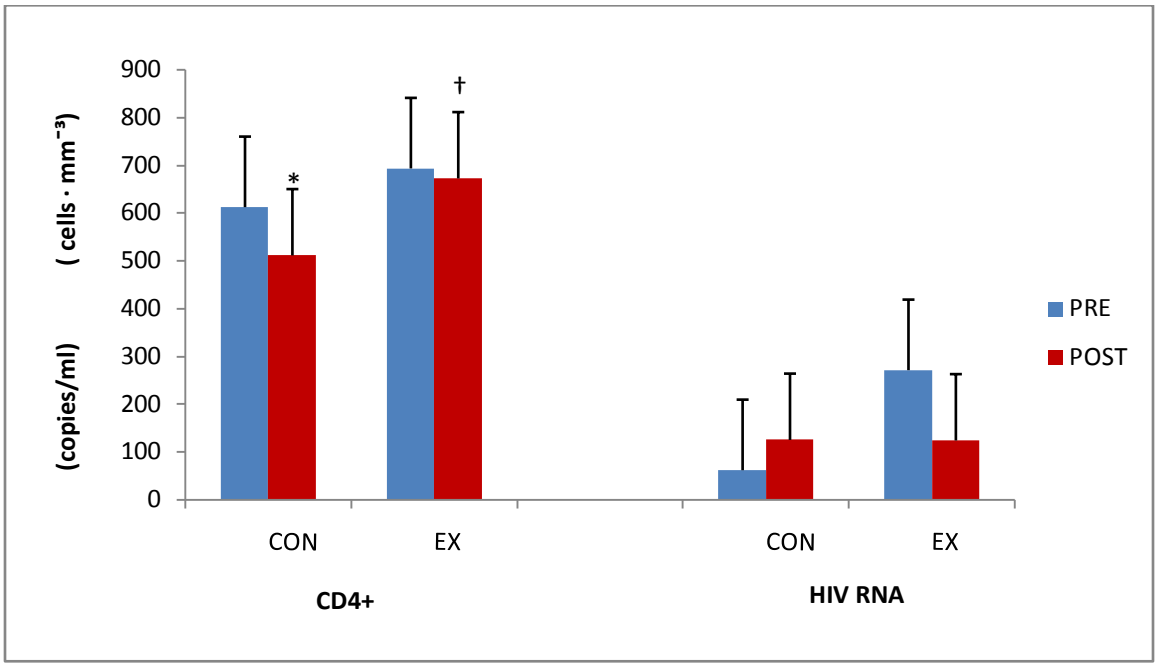
Figure 2. Changes in One-Repetition Maximum (1RM) for Chest and Legs in Control and Exercise Groups at Baseline and Following the Intervention



LBS: pounds, 1RM CHEST: 1 repetition maximum for chest press, 1RM LEGS: 1 repetition maximum for leg press, CON: control subjects, EX: exercise subjects, PRE: baseline evaluation, POST: immediate post-intervention 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)

Figure 3. Changes in CD4+ Cell Count and HIV RNA Viral Load in Control and Exercise Groups at Baseline and Following the Intervention



CD4+: CD4+ T cell count, HIV RNA: HIV RNA viral load, CON: control subject, EX: exercise subjects, PRE: baseline evaluation, POST: immediate post- intervention 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)

References

Allain, C. C., Poon, L. S., Chan, C. S., Richmond, W., & Fu, P. C. (1974). Enzymatic determination of total serum cholesterol. *Clin.Chem., 20,* 470-475.

American College of Sports Medicine. (2006). ACSM's Guidelines for Exercise Testing and Prescription; seventh edition.
Ref Type: Catalog

Berg, K. M., Demas, P. A., Howard, A. A., Schoenbaum, E. E., Gourevitch, M. N., & Arnsten, J. H. (2004). Gender differences in factors associated with adherence to antiretroviral therapy. *J Gen.Intern.Med., 19,* 1111-1117.

Birk, T. J., MacArthur, R. D., Lipton, L. M., & Levine, S. D. (2002). Aerobic exercise training fails to lower hypertriglyceridemia levels in persons with advanced HIV-1 infection. *J Assoc Nurses AIDS Care, 13,* 20-24.

Blair, S. N., Haskell, W. L., Ho, P., Paffenbarger, R. S., Jr., Vranizan, K. M., Farquhar, J. W. et al. (1985). Assessment of habitual physical activity by a seven-day recall in a community survey and controlled experiments. *Am.J Epidemiol., 122,* 794-804.

Bogart, L. M., Kelly, J. A., Catz, S. L., & Sosman, J. M. (2000). Impact of medical and nonmedical factors on physician decision making for HIV/AIDS antiretroviral treatment. *J Acquir.Immune.Defic.Syndr., 23,* 396-404.

Bopp, C. M., Phillips, K. D., Fulk, L. J., & Hand, G. A. (2003). Clinical implications of therapeutic exercise in HIV/AIDS. *J Assoc.Nurses AIDS Care, 14,* 73-78.

Cade, W. T., Fantry, L. E., Nabar, S. R., Shaw, D. K., & Keyser, R. E. (2003). A comparison of Qt and a-vO2 in individuals with HIV taking and not taking HAART. *Med.Sci.Sports Exerc., 35,* 1108-1117.

Carr, A., Samaras, K., Thorisdottir, A., Kaufmann, G. R., Chisholm, D. J., & Cooper, D. A. (1999). Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. *Lancet, 353,* 2093-2099.

Church, T. S., Blair, S. N., Cocreham, S., Johannsen, N., Johnson, W., Kramer, K. et al. (2010). Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: a randomized controlled trial. *JAMA, 304,* 2253-2262.

Ciccolo, J. T., Jowers, E. M., & Bartholomew, J. B. (2004). The benefits of exercise training for quality of life in HIV/AIDS in the post-HAART era. *Sports Med., 34,* 487-499.

Cunningham, W. E., Hays, R. D., Duan, N., Andersen, R., Nakazono, T. T., Bozzette, S. A. et al. (2005). The effect of socioeconomic status on the survival of people receiving care for HIV infection in the United States. *J Health Care Poor Underserved, 16,* 655-676.

d'Arminio, M. A., Lepri, A. C., Rezza, G., Pezzotti, P., Antinori, A., Phillips, A. N. et al. (2000). Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients. I.CO.N.A. Study Group. Italian Cohort of Antiretroviral-Naive Patients. *AIDS, 14,* 499-507.

de, W. S., Sabin, C. A., Weber, R., Worm, S. W., Reiss, P., Cazanave, C. et al. (2008). Incidence and risk factors for new-onset diabetes in HIV-infected patients: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. *Diabetes Care, 31,* 1224-1229.

Dishman, R. K. & Steinhardt, M. (1988). Reliability and concurrent validity for a 7-d re-call of physical activity in college students. *Med.Sci.Sports Exerc., 20,* 14-25.

Douglas, J. G., Bakris, G. L., Epstein, M., Ferdinand, K. C., Ferrario, C., Flack, J. M. et al. (2003). Management of high blood pressure in African Americans: consensus statement of the Hypertension in African Americans Working Group of the International Society on Hypertension in Blacks. *Arch.Intern.Med., 163,* 525-541.

Dube, M. P. & Sattler, F. R. (1998). Metabolic complications of antiretroviral therapies. *AIDS Clin.Care, 10,* 41-44.

Fairfield, W. P., Treat, M., Rosenthal, D. I., Frontera, W., Stanley, T., Corcoran, C. et al. (2001). Effects of testosterone and exercise on muscle leanness in eugonadal men with AIDS wasting. *J.Appl.Physiol, 90,* 2166-2171.

Fichtenbaum, C. J., Clifford, D. B., & Powderly, W. G. (1995). Risk factors for dideoxynucleoside-induced toxic neuropathy in patients with the human immunodeficiency virus infection. *J Acquir.Immune.Defic.Syndr.Hum.Retrovirol., 10,* 169-174.

Fillipas, S., Oldmeadow, L. B., Bailey, M. J., & Cherry, C. L. (2006). A six-month, supervised, aerobic and resistance exercise program improves self-efficacy in people with human immunodeficiency virus: a randomised controlled trial. *Aust.J.Physiother., 52,* 185-190.

Friedewald, W. T., Levy, R. I., & Fredrickson, D. S. (1972). Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin.Chem., 18,* 499-502.

Garratt, A., Schmidt, L., Mackintosh, A., & Fitzpatrick, R. (2002). Quality of life measurement: bibliographic study of patient assessed health outcome measures. *BMJ, 324,* 1417.

Halbert, J. A., Silagy, C. A., Finucane, P., Withers, R. T., Hamdorf, P. A., & Andrews, G. R. (1997). The effectiveness of exercise training in lowering blood pressure: a meta-analysis of randomised controlled trials of 4 weeks or longer. *J Hum.Hypertens., 11,* 641-649.

Hand, G. A., Phillips, K. D., Dudgeon, W. D., William, L. G., Larry, D. J., & Burgess, S. E. (2008). Moderate intensity exercise training reverses functional aerobic impairment in HIV-infected individuals. *AIDS Care, 20,* 1066-1074.

Hirsch, H. H. & Battegay, M. (2002). Lipodystrophy syndrome by HAART in HIV-infected patients: manifestation, mechanisms and management. *Infection, 30,* 293-298.

Hogg, R. S., Yip, B., Chan, K. J., Wood, E., Craib, K. J., O'Shaughnessy, M. V. et al. (2001). Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. *JAMA, 286,* 2568-2577.

Horwath, E. (2011). Psychiatric and neuropsychiatric manifestations of HIV infection. *J Int Assoc Physicians AIDS Care, 1,* S3-15.

Johnson, J. E., Anders, G. T., Blanton, H. M., Hawkes, C. E., Bush, B. A., McAllister, C. K. et al. (1990). Exercise dysfunction in patients seropositive for the human immunodeficiency virus. *Am.Rev.Respir.Dis., 141,* 618-622.

Justman, J. E., Benning, L., Danoff, A., Minkoff, H., Levine, A., Greenblatt, R. M. et al. (2003). Protease inhibitor use and the incidence of diabetes mellitus in a large cohort of HIV-infected women. *J Acquir.Immune.Defic.Syndr., 32,* 298-302.

Kass, N. E., Munoz, A., Chen, B., Zucconi, S. L., & Bing, E. G. (1994). Changes in employment, insurance, and income in relation to HIV status and disease progression. The Multicenter AIDS Cohort Study. *J Acquir.Immune.Defic.Syndr., 7,* 86-91.

Keyser, R. E., Peralta, L., Cade, W. T., Miller, S., & Anixt, J. (2000). Functional aerobic impairment in adolescents seropositive for HIV: a quasiexperimental analysis. *Arch.Phys.Med.Rehabil., 81,* 1479-1484.

LaPerriere, A., Antoni, M. H., Ironson, G., Perry, A., McCabe, P., Klimas, N. et al. (1994). Effects of aerobic exercise training on lymphocyte subpopulations. *Int J Sports Med., 15 Suppl 3,* S127-S130.

Leserman, J., Jackson, E. D., Petitto, J. M., Golden, R. N., Silva, S. G., Perkins, D. O. et al. (1999). Progression to AIDS: the effects of stress, depressive symptoms, and social support. *Psychosom.Med., 61,* 397-406.

Lo, J. C., Mulligan, K., Tai, V. W., Algren, H., & Schambelan, M. (1998). "Buffalo hump" in men with HIV-1 infection. *Lancet, 351,* 867-870.

Lox, C. L., McAuley, E., & Tucker, R. S. (1996). Aerobic and resistance exercise training effects on body composition, muscular strength, and cardiovascular fitness in an HIV-1 population. *Int J Behav.Med., 3,* 55-69.

MacArthur, R. D., Levine, S. D., & Birk, T. J. (1993c). Supervised exercise training improves cardiopulmonary fitness in HIV-infected persons. *Med.Sci.Sports Exerc., 25,* 684-688.

Manson, J. E., Hu, F. B., Rich-Edwards, J. W., Colditz, G. A., Stampfer, M. J., Willett, W. C. et al. (1999). A prospective study of walking as compared with vigorous exercise in the prevention of coronary heart disease in women. *N.Engl.J Med., 341,* 650-658.

McHorney, C. A., Ware, J. E., Jr., & Raczek, A. E. (1993). The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med.Care, 31,* 247-263.

Miller, K. D., Jones, E., Yanovski, J. A., Shankar, R., Feuerstein, I., & Falloon, J. (1998). Visceral abdominal-fat accumulation associated with use of indinavir. *Lancet, 351,* 871-875.

Mustafa, T., Sy, F. S., Macera, C. A., Thompson, S. J., Jackson, K. L., Selassie, A. et al. (1999). Association between exercise and HIV disease progression in a cohort of homosexual men. *Ann.Epidemiol., 9,* 127-131.

Myers, J., Prakash, M., Froelicher, V., Do, D., Partington, S., & Atwood, J. E. (2002). Exercise capacity and mortality among men referred for exercise testing. *N.Engl.J Med., 346,* 793-801.

O'Brien, K., Nixon, S., Tynan, A. M., & Glazier, R. H. (2004). Effectiveness of aerobic exercise in adults living with HIV/AIDS: systematic review. *Med.Sci.Sports Exerc., 36,* 1659-1666.

Palella, F. J., Jr., Delaney, K. M., Moorman, A. C., Loveless, M. O., Fuhrer, J., Satten, G. A. et al. (1998). Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N.Engl.J.Med., 338,* 853-860.

Prentiss, D., Power, R., Balmas, G., Tzuang, G., & Israelski, D. M. (2004). Patterns of marijuana use among patients with HIV/AIDS followed in a public health care setting. *J Acquir.Immune.Defic.Syndr., 35,* 38-45.

Reilly, C. A., Holzemer, W. L., Henry, S. B., Slaughter, R. E., & Portillo, C. J. (1997). A comparison of patient and nurse ratings of human immunodeficiency virus-related signs and symptoms. *Nurs.Res., 46,* 318-323.

Rigsby, L. W., Dishman, R. K., Jackson, A. W., Maclean, G. S., & Raven, P. B. (1992). Effects of exercise training on men seropositive for the human immunodeficiency virus-1. *Med.Sci.Sports Exerc., 24,* 6-12.

Robinson, F. P., Quinn, L. T., & Rimmer, J. H. (2007). Effects of high-intensity endurance and resistance exercise on HIV metabolic abnormalities: a pilot study. *Biol.Res.Nurs., 8,* 177-185.

Rosen, M. J., Sorkin, J. D., Goldberg, A. P., Hagberg, J. M., & Katzel, L. I. (1998). Predictors of age-associated decline in maximal aerobic capacity: a comparison of four statistical models. *J Appl.Physiol, 84,* 2163-2170.

Rosenfeld, B., Breitbart, W., Stein, K., Funesti-Esch, J., Kaim, M., Krivo, S. et al. (1999a). Measuring desire for death among patients with HIV/AIDS: the schedule of attitudes toward hastened death. *Am.J.Psychiatry, 156,* 94-100.

Roubenoff, R. & Wilson, I. B. (2001). Effect of resistance training on self-reported physical functioning in HIV infection. *Med.Sci.Sports Exerc., 33,* 1811-1817.

Ryan, J. G. (1995). Who uses alternative therapies and what happens to them? Outcomes from the use of AIDS alternative therapies among people infected with HIV: a synthesis of the medical literature. *AHSR FHSR Annu Meet Abstr Book, 12,* 82-83.

Schlenzig, C., Jager, H., & Rieder, H. (1989). *Supervised physical exercise leads to psychological and immunological improvements in pre-AIDS patients.* Montreal, Canada: Proceedings of the 5th International AIDS Conference.

Seguin, R. & Nelson, M. E. (2003). The benefits of strength training for older adults. *Am.J Prev.Med., 25,* 141-149.

Smith, B. A., Neidig, J. L., Nickel, J. T., Mitchell, G. L., Para, M. F., & Fass, R. J. (2001). Aerobic exercise: effects on parameters related to fatigue, dyspnea, weight and body composition in HIV-infected adults. *AIDS, 15,* 693-701.

Stoll, T., Kauer, Y., Buchi, S., Klaghofer, R., Sensky, T., & Villiger, P. M. (2001). Prediction of depression in systemic lupus erythematosus patients using SF-36 Mental Health scores. *Rheumatology.(Oxford), 40,* 695-698.

Stringer, W. W. (2000). Mechanisms of exercise limitation in HIV+ individuals. *Med.Sci.Sports Exerc., 32,* S412-S421.

Stringer, W. W., Berezovskaya, M., O'Brien, W. A., Beck, C. K., & Casaburi, R. (1998). The effect of exercise training on aerobic fitness, immune indices, and quality of life in HIV+ patients. *Med.Sci.Sports Exerc., 30,* 11-16.

Tamesis, B., Stelken, A., Byers, S., Shaw, L., Younis, L., Miller, D. D. et al. (1993). Comparison of the Asymptomatic Cardiac Ischemia Pilot and modified

Asymptomatic Cardiac Ischemia Pilot versus Bruce and Cornell exercise protocols. *Am.J Cardiol., 72,* 715-720.

Terry, L., Sprinz, E., & Ribeiro, J. P. (1999). Moderate and high intensity exercise training in HIV-1 seropositive individuals: a randomized trial. *Int J Sports Med., 20,* 142-146.

Terry, L., Sprinz, E., Stein, R., Medeiros, N. B., Oliveira, J., & Ribeiro, J. P. (2006). Exercise training in HIV-1-infected individuals with dyslipidemia and lipodystrophy. *Med.Sci.Sports Exerc., 38,* 411-417.

The U.S.Department of Health and Human Services (2008). *Physical Activity Guidelines for Americans*.

Thoni, G. J., Fedou, C., Brun, J. F., Fabre, J., Renard, E., Reynes, J. et al. (2002). Reduction of fat accumulation and lipid disorders by individualized light aerobic training in human immunodeficiency virus infected patients with lipodystrophy and/or dyslipidemia. *Diabetes Metab, 28,* 397-404.

van, S. G., Nyamathi, A., Carpio, F., Pearce, D., Garcia-Teague, L., Herrera, G. et al. (2005). Effects of a treatment adherence enhancement program on health literacy, patient-provider relationships, and adherence to HAART among low-income HIV-positive Spanish-speaking Latinos. *AIDS Patient.Care STDS., 19,* 745-759.

Warnick, G. R., Benderson, J., & Albers, J. J. (1982). Dextran sulfate-Mg2+ precipitation procedure for quantitation of high-density-lipoprotein cholesterol. *Clin.Chem., 28,* 1379-1388.

Whipple, R. H., Wolfson, L. I., & Amerman, P. M. (1987). The relationship of knee and ankle weakness to falls in nursing home residents: an isokinetic study. *J Am.Geriatr.Soc., 35,* 13-20.

Yarasheski, K. E., Tebas, P., Stanerson, B., Claxton, S., Marin, D., Bae, K. et al. (2001). Resistance exercise training reduces hypertriglyceridemia in HIV-infected men treated with antiviral therapy. *J.Appl.Physiol, 90,* 133-138.

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