

**Creatine Phosphokinase Levels in HIV-Seropositive
Individuals after a Single Bout of Isokinetic
Resistance Exercise**

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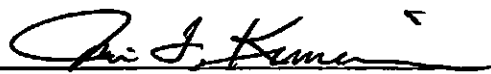
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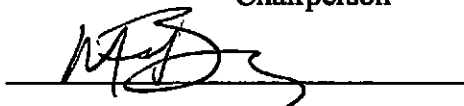
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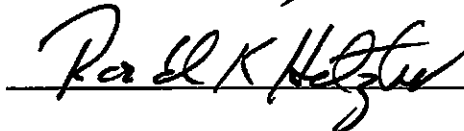
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Acknowledgements

One thing no one has ever doubted in me is my pride. I have always been proud of what I have accomplished, where I am from, and who I am. Hawai'i is no different. I may not always make the best choices, but I see what I have done here as a great accomplishment for me and the people I have met along the way. I am proud of where I now come from. The University of Hawai'i offered me experiences I cannot find anywhere else and I feel I have left my mark. The state of Hawai'i, in all of its beauty, has knocked me down to simply build me back up again in new surroundings. Being so far away from home I learned to find comfort in myself and ask for help from others. I have made relationships that will last a lifetime and found a part of myself I did not know existed. I love all of you and can never thank you enough. I am still proud of who I am because of your friendship, love and support. Carey, Kelly, Kristen, Kyle, Ryan, Kaori, Nyki, Cris, and Iris (that's right... I said IRIS); How could I ask for more?

'O ka hilinai'i ka 'imi 'ana i kahi pōhihihi a ka puka aku 'ana me ka 'ike.

How can you lose your song; when you have sung it for so long
 How can you forget your dance; when that dance is all you ever had
 It must be true; You can't separate the two.
 It's impossible to do; just like the salt in the stew
 It's all a part of you
 One thing that life cannot do
 It can't take your salt from you

Courtney; Thank you for being my best friend. You are beautiful and I can't wait to see you again. Reggie; no matter what may happen down the road, I am a better person because of you being in my life. To both, thank you for your unconditional love. It is only the beginning.

Daddy, Mama, and Jacy; Thank you for creating the foundation for me to have great success in life. You helped me to build a life I never could have imagined for myself. And still I am amazed by the strength of this family. Thank you for picking me up when I am down and enjoying life with me when I am up. My success is OUR success. Thank you for teaching me to be passionate in everything I do and standing by my side. Thank you most of all for your unconditional love. It is the only love that survives.

Although I am leaving, a little piece of me will stay in the middle of the Pacific Ocean. I have been in the land of Aloha and the land of Southern Hospitality. And now...

I AM ALL PAU!! MAMA I'M COMIN' HOME!!

Abstract

Context: Human Immunodeficiency Virus (HIV) is a life long immunosuppressive disease that leads to aerobic and anaerobic deconditioning, and diminished capacity to function independently in society, Acquired Immunodeficiency Syndrome (AIDS), the risk of AIDS wasting, and death. Normal elevations of creatine phosphokinase (CK) in HIV-Seropositive individuals, even at rest, are not consistently associated with varied symptoms of the disease; however it is the most reliable muscle damage quantifier. Additionally, investigation of an acute high-intensity resistance exercise bout on HIV-Seropositive individuals is limited and may be detrimental to HIV-Seropositive individuals by suddenly activating the immune system, thereby increasing HIV replication

Objective: To investigate the effects of a single bout of high-intensity concentric resistance exercise and CK in the HIV-Seropositive population.

Design: Data were analyzed using analysis of variance (ANOVA) for peak torque (PT) knee flexion and extension, body mass index (BMI), and percent body fat, 2 x 5 repeated measures ANOVA for CK levels, and 2 x 3 repeated measures ANOVA for number of repetitions to 50% fatigue per set.

Setting: AIDS clinic and University athletic training lab

Participants: 13 HIV-Seropositive participants (two females and eleven males; age = 44.5 ± 8.5 years, BMI = 25.2 ± 3.7) and six HIV-negative participants (one female and five males; age = 40.5 ± 4.0 years, BMI = 30.7 ± 2.5).

Intervention(s): Participants performed three sets of isokinetic knee flexion and extension to 50% fatigue on the Biodex 3 systems.

Main Outcome Measure(s): Serum CK levels pre-test and post-exercise at 24, 48, 96, and 168 hours. Peak Torque knee flexion and extension, number of repetitions to fatigue, BMI, and percent body fat were measured pre-exercise.

Results: No differences were revealed in CK levels regardless of group ($P = 0.09$) and no interactions between groups and CK collection times ($P = 0.66$). No difference in PT flexion or extension for the HIV-Seropositive (54.2 ± 22.2 and 95.4 ± 37.8 respectively) and the HIV-Negative (124.7 ± 41.9 , $P = 0.15$ and 70.2 ± 19.4 , $P = 0.15$) groups. Percent body fat and BMI were significantly lower in the HIV-Seropositive group (25.2 ± 3.7 , $P = 0.01$; 25.4 ± 7.8 , $P = 0.02$) than the HIV-Negative group (30.7 ± 2.7 ; 34.4 ± 4.7).

Conclusions: A single acute bout of anaerobic concentric resistance exercise did not sufficiently cause a significant increase in CK levels in HIV-Seropositive individuals.

Key Words: HIV and anaerobic exercise, HIV and creatine phosphokinase

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PART I

Introduction

Human Immunodeficiency Virus (HIV) is a life long immunosuppressive disease that leads to aerobic and anaerobic deconditioning, and diminished capacity to function independently in society, Acquired Immunodeficiency Syndrome (AIDS), the risk of AIDS wasting, and death (Roubenoff, Skolnik et al. 1999). Acquired Immunodeficiency Syndrome wasting is defined as the involuntary loss of more than 10% of body weight and at least 30 days of diarrhea, weakness, or vomiting. The occurrence of wasting can begin in the early stages of HIV (>200 cells/mm³) and may continue to progress rapidly. Low food intake, poor nutrition absorption, and altered metabolism may all contribute to the level of wasting. (Mangili, Murman et al. 2006)

Highly Active Antiretroviral Therapy (HAART) is the best known treatment for HIV and AIDS. These medications decrease mortality and the frequency of opportunistic infections in HIV and AIDS patients. Delayed onset of AIDS in HIV-Seropositive patients via HAART, occurs when the virus is attacked at different stages in its life cycle, thereby preventing HIV multiplication. Antiretroviral medications are typically utilized first when the CD4 cell count drops below 350 cells per micro liter (μL). (Manji, Harrison et al. 1993; Simpson, Citak et al. 1993; McDermott, Shevitz et al. 2001) Lipodystrophy or lipoatrophy is defined as a group of conditions caused by defective metabolism of fat, resulting in the absence of subcutaneous fat and is a well know side-effect of HAART (Corless, Kirksey et al. 2005). Unfortunately, antiretroviral therapy also impairs mitochondrial function that

contributes to muscle myopathy (Manji, Harrison et al. 1993; Simpson, Citak et al. 1993; McDermott, Shevitz et al. 2001; Polsky, Kotler et al. 2001; Authier, Chariot et al. 2005).

Muscle myopathy can be quantified via the release of intracellular enzymes into the circulation. Although this method is not proven to be equivalent to muscle damage at all times, the most commonly utilized serum indicator of muscle damage is creatine phosphokinase (CK). This enzyme facilitates the transfer of high-energy phosphate groups from creatine phosphate to adenosine diphosphate, yielding creatine and adenosine triphosphate (ATP). The ATP is utilized for the immediate energy needs of metabolically active cells. (Hortobagyi and Denahan 1989)

Creatine phosphokinase is principally contained within the plasma membrane of skeletal muscle, and also cardiac muscle and brain cells. Damage to any of these structures stimulates its release into the circulation, via cell death or increased membrane permeability. Creatine phosphokinase release may be acute and severe, as in rhabdomyolysis following muscle ischemia, crush injury or heat stroke, and to a lesser extent, cardiac damage following myocardial infarction. Chronic low-grade to moderate elevations in CK are seen in myopathies such as muscular dystrophy. (Hortobagyi and Denahan 1989; Ercan and Grossman 2003)

The magnitude and duration of CK elevation in response to exertion varies widely according to age, gender, race, activity level, and activity mode. (Schwane, Buckley et al. 2000; Manfredi, Motta et al. 2002). Creatine phosphokinase release is more dramatic in high intensity activity than low intensity long duration activity.

Consequently, anaerobic resistance exercise generates greater CK releases than aerobic endurance exercise indicating that more muscle damage has occurred. (Hortobagyi and Denahan 1989). Concentric muscle activity results in an intermediate time course of CK elevation. Eccentric muscle activity (forced muscle lengthening) creates a delayed CK elevation which may be sustained 7-10 days following inducement. (Hyatt and Clarkson 1998; Prou, Guevel et al. 1999; Stupka, Tarnopolsky et al. 2001; Lavender and Nosaka 2006) This pattern of CK release contrasts that of intense aerobic activity, with peaks seen within 24-48 hours and normalization after 36-96 hours. Sequentially, there appears to be a protective training effect whereby the magnitude of CK released following a given activity lessens over time as an individual repeatedly performs the exercise. (Vincent and Vincent 1997; Cleary, Kimura et al. 2002)

Creatine phosphokinase levels in HIV-infected individuals appear to be higher than the general population, even at rest. These elevations are not consistently associated with varied symptoms of the disease; however it is the most reliable muscle damage quantifier. (Dalakas, Illa et al. 1990; Chariot and Gherardi 1995; Chariot and Gherardi 1995; Manfredi, Motta et al. 2002) Results of a nine month prospective study of 875 HIV-Seropositive subjects receiving HAART therapy revealed a 15% incidence of CK abnormalities. The majority of participants had isolated CK elevations, and thirty-three subjects repeatedly revealed abnormal values. Significant CK elevations seen in males were influenced by age, overall length of antiretroviral therapy, CD4+ lymphocyte count, and HIV viral load. Symptoms such

as muscle weakness and fatigue were less prevalent among individuals with elevations in CK than to individuals without CK elevations. (Manfredi, Motta et al. 2002) Increased Zidovudine (AZT) was seen in subjects with CK elevations. These elevations were most pronounced in therapy regimen combinations of AZT and zalcitabine for twenty weeks or greater. However, symptoms of muscle damage again did not reliably correlate to CK abnormalities. (Simpson, Katzenstein et al. 1998)

The effect of various forms of exercise on HIV-infected individuals has been studied in other contexts. These studies involved aerobic exercise interventions, with less emphasis on resistance training. Meta-analysis of randomized controlled trials involving the effects of aerobic training in HIV-Seropositive subjects indicated that moderate intensity exercise was well tolerated, with cardiopulmonary and psychological benefits. (Lawless, Jackson et al. 1995; LaPerriere, Klimas et al. 1997; Shephard 1998) No adverse effects on CD4+ lymphocyte count or virologic control were observed. Combined aerobic exercise and resistance training have been shown to improve cardiopulmonary status without influencing HIV disease progression (Perna, LaPerriere et al. 1999; O'Brien, Nixon et al. 2004; Nixon, O'Brien et al. 2005). Individual studies employing less rigorous methodology have shown exercise-related improvements in serum lipids, blood pressure and body composition (primarily decreased abdominal fat), as well as slowing disease progression to AIDS (Jones, Doran et al. 2001; Scevola, Di Matteo et al. 2003). The combination of resistance training and androgen therapy has been shown to improve muscle strength

and lean body mass in some HIV-infected males (Evans, Roubenoff et al. 1998; Strawford, Barbieri et al. 1999; Bhasin, Storer et al. 2000).

Additionally, investigation of an acute high-intensity resistance exercise bout on HIV-Seropositive individuals is limited and may be detrimental to HIV-Seropositive individuals by suddenly activating the immune system, thereby increasing HIV replication (Roubenoff, Skolnik et al. 1999). Therefore, the purpose of this study was to investigate the effects of high-intensity concentric resistance exercise and CK in HIV-Seropositive individuals. The hypotheses of this study were that there will be no difference in concentric resistance exercise results of HIV-Seropositive and HIV-negative individuals in: CK levels, peak torque knee flexion and extension, fatigue via repetitions, and body composition values.

Methodology

Research Design

A 2 x 5 analysis of variance (ANOVA) with repeated measures was used to analyze CK data, and a 2 x 3 ANOVA with repeated measures was used to analyze the number of repetitions to 50% fatigue over time. Analysis of variance tables were used to compare BMI, percent body fat, and peak torque production between groups. The independent variable for the above analyses was HIV-infection status. The dependent variables were CK level, knee peak torque flexion and extension, number of repetitions to fatigue, BMI, and percent body fat.

Participants

Prior to performing in the study, participants were screened for medical pathologies via a risk level assessment pre-participation physical examination (see Appendix A). A signed written informed consent approved by the University Committee on Human Studies was obtained from all subjects (see Appendix B). Participants were excluded from the protocol if they had a history of medical illnesses (cardiac, thyroid, rheumatologic, renal, neurologic, muscle, or other severe disease) which would limit their exercise tolerance or took medications or substances associated with CK level abnormalities (Table 1).

Table 1. Exclusionary Substances/Medications

Current illicit substance abuse	
Alcohol in excess of 20g/day	
Anabolic steroid or ergogenic compounds (i.e. creatine)	
<u>Myopathic Medications</u>	
Amiodarone	Lipid-lowering agents
Antibiotics	HMG CoA reductase inhibitors
Daptomycin	Fenofibrates
Corticosteroids (systemic)	Niacin
Colchicine	Isoniazid
Chloroquine/hydroxychloroquine	Pentamidine
D-penicillamine	Lamotrigine
Beta Blockers	Valproic Acid
Cimetidine	Neuroleptics/Phenothiazines

HIV-Seropositive subjects were also required to be on a stable regimen of nucleoside reverse transcriptase inhibitor (NRTI) -containing antiretroviral therapy and maintaining a HAART regimen for at least three months prior to the study. Research inclusion required CD4+ lymphocyte count to be greater than or equal to 200×10^6 cells/L and viral load less than 1000 copies/mL within three months of screening.

Participants were 13 HIV-Seropositive (two female and eleven male) and six HIV-negative (one female and five male) volunteers. None of the participants exercised more than two times a week or had engaged in strength training in the preceding six months (Table 2).

Table 2. Subject HIV status, age, BMI, percent body fat (DEXA), and CK baseline level (Means \pm SD)

HIV Status	Subjects (n)	Age (yr)	CK Baseline (IU/L)	BMI	Body Fat (%)
Seropositive	13	44.5 \pm 8.5	210.9 \pm 181.1	25.2 \pm 3.7	25.4 \pm 7.8
Negative	6	40.5 \pm 4.0	146.3 \pm 38.0	30.7 \pm 2.5	34.4 \pm 4.7

Body Composition

Body composition of participants meeting eligibility criteria was assessed by Dual Energy X-ray Absorptiometry (DEXA) scan using a GE Lunar Prodigy Advance densitometer (GE Healthcare, Waukesha, WI). The machine was composed of a low-radiation source which emitted x-rays at two different photon-energies from the generator to a scanning table. (Pietrobelli, Wang et al. 1998) The differential attenuation of these x-rays through the body allowed for accurate calculation of body composition. Dual Energy X-ray Absorptiometry was a three compartment assessment method that involved estimation of fat and lean tissue components and measurement of bone mineral density. Whereas precision for bone mineral density has been calculated at less than 1%, variation in lean body mass (bone + muscle) may be somewhat greater, between 4.9 to 5.3%. (Genton, Hans et al. 2002). The principal investigator performed all DEXA scans to increase reliability. Body composition analysis was accomplished using the standard software accompanying the DEXA, encore 2004 for Windows, version 8.1 (GE Healthcare, Waukesha, WI).

Isokinetic Resistance Exercise

The Biodex Multi-Joint System 3 dynamometer (Biodex Medical Systems, Inc., Shirley, New York) was used to assess unilateral fatigue of the quadriceps and hamstrings muscles. Participants were tested in a seated position with 85 degrees of hip flexion. Seatback depth was adjusted with a three centimeter space between the popliteal fossa and the edge of the chair. The axis of rotation of the dynamometer was aligned 1 ½ inches from the lateral femoral epicondyle of the tested knee. The distal lower leg was fixed to the lever arm of the dynamometer 3.12 cm proximal to the distal end of the medial malleolus. Participants were secured to the chair via belts at the waist, thigh and diagonally across the torso with the arms crossed and the palms on opposite shoulders to minimize excessive upper body movement and muscular substitution. All positioning followed the Biodex 3 System guidelines. A goniometer was used to set knee range of motion at 0 degree of extension and 100 degrees of flexion. Participants underwent a familiarization and warm-up protocol consisting of an explanation of the exercise protocol (Appendix C), ten repetitions at 30 – 40% effort and five repetitions at 100% effort. This was followed by a two-minute rest period prior to beginning three maximal effort test sets to 50% fatigue. The participant was asked which leg would be used to kick a ball thrown to them, to determine “leg dominance”. This leg was used with the exception of one subject due to previous knee surgery.

Exercise Protocol

Participants were introduced to the University of Hawai'i, Athletic Training Laboratory, familiarized with testing procedures, and asked to maintain normal activity throughout the study period. Participants completed a three set exercise protocol at 180 degrees/second, with 120 seconds of rest time between sets, for the CK levels to reach homeostasis. Peak torque values were determined during the warm-up used to calculate 50% peak torque fatigue. During each of the three sets, participants were instructed to provide maximal work efforts until told to stop by the investigator. Sets were completed when the participants' maximum torque output for both knee flexion and extension was decreased to 50% peak torque for three consecutive repetitions of the quadriceps and the hamstrings. After the final set each participant was helped off the Biodex 3 and provided water and quadriceps and hamstrings stretching assistance, by the certified athletic trainer. Instructions for home stretching were given.

Criterion Measures

A blood sample of 44-59 cc was taken within 24 hours of the Biodex 3 exercise protocol. Pregnancy tests were performed on female participants via a 15 cc blood sample and urine analysis. Blood samples post-exercise and at 24, 48, 96 and 168-hours were used to determine CK activity levels. Samples were analyzed with an automated paramagnetic chemiluminescent sandwich immunoassay utilizing the UniCel DxI 800 Access® Immunoassay System (Beckman-Coulter, Fullerton, CA).

Each specimen was collected in a serum-separating tube (SST). Baseline chemistries and lactate were also obtained through Diagnostic Laboratory Services (DLS) and collected in SST and sodium fluoride-containing specimen tubes, respectively.

Statistical Analyses

Statistical Analysis System (SAS) Version 9.0 English software package (SAS Institute Inc., Cary, North Carolina, USA) was used for analysis of the data. Alpha levels were set at $P < 0.05$.

Results

Raw data for group and dependent variables are presented in Appendix D. Creatine Phosphokinase data analyses (Appendix E) revealed no significant main effect or interaction effect between groups (HIV-Seropositive and HIV-Negative) and blood collection over time. Fatigue data analyses (Appendix F) indicated a significant main effect for number of repetitions to 50% fatigue regardless of group (Table 3). Helmert post-Hoc test results revealed significant decreases in number of repetitions between set one and two, three; and set two and three. Isokinetic concentric data analysis revealed no significant difference between groups in peak torque production of knee flexion and extension. Body composition data analyses (Appendix G) indicated that percent body fat and BMI of the HIV-Seropositive group were significantly lower than the HIV-Negative group (Table 4).

Table 3. Summary of CK over time and Number of Repetitions to 50% Fatigue Per Set Measurement Data (Mean ± SD)

HIV-Status	CK Levels (IU/L)					Number of Repetitions to Fatigue		
	0 hrs	24 hrs	48hrs	96hrs	186hrs	Set 1	Set 2	Set 3
Seropositive	210.9±188.5	786.6±1181.2	551.8±586.8	548.7±792.6	190.8±121.2	29.8±6.6	23.1±5.4	19.2±3.6
Negative	146.3 ± 41.7	387.8 ± 314.2	287.5±241.3	320.7±251.4	204.3±106.7	25.0±7.3	21.2±6.7	17.0±6.6
F and P-Value	2.14 and 0.09					24.57 and <.0001**		
**Significant difference between HIV-Seropositive and HIV-Negative; $p < 0.05$								

Table 4. Summary of peak torque flexion and extension values ANOVAs and Measurement Data

(Mean \pm SD)

HIV-Status	Peak Torque Extension (ft-lbs)	Peak Torque Flexion (ft-lbs)	BMI	Percent Body Fat (DEXA)
Seropositive	95.4 \pm 37.8	54.2 \pm 22.2	25.2 \pm 3.8	25.4 \pm 7.8
Negative	124.7 \pm 41.9	70.2 \pm 19.4	30.7 \pm 2.7	34.4 \pm 4.7
F-Value	2.31	2.30	9.98	6.65
P-Value	0.15	0.15	0.01**	0.02**
**Significant difference between HIV-Seropositive and HIV-Negative; $p < 0.05$				

Discussion

The major finding of the present study was that a single bout of anaerobic concentric resistance exercise did not increase CK levels in HIV-Seropositive individuals (Figure 1). To our knowledge, this is the first study that involved investigation of a single bout of anaerobic resistance exercise and CK levels in HIV-Seropositive patients. Consequently, our results contrast previous single and multiple bout anaerobic resistance exercise protocols that revealed significant increases in CK levels of HIV-negative individuals (Karamizrak, Ergen et al. 1994; Dolezal, Potteiger et al. 2000). This difference may be due to the type and length of exercise as well as higher sample sizes in these studies.

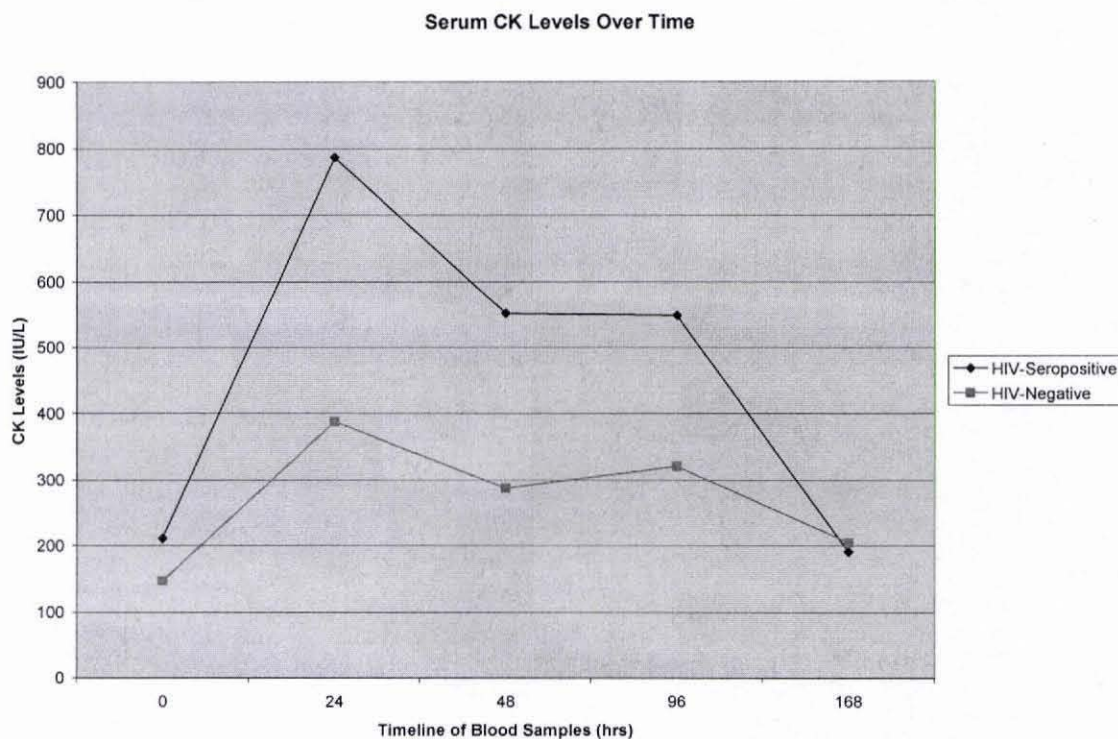


Figure 1. CK Level Activity Over Time Values HIV-Seropositive and HIV-Negative (Mean)

The exercise protocol employed in the present study was based on studies by Gibala et al. (1995) and Staron et al. (1992). Gibala et al. (1995) showed significant CK elevations in healthy individuals following the performance of one bout of resisted exercise to the elbow flexors with eight sets of eight repetitions at a pace of two seconds per repetition and 80% one-repetition maximum (RM). Staron et al. (1992) also revealed significant CK increases in healthy individuals following an eight-week training protocol consisting of two warm-up sets followed by three sets to failure or fatigue of either 6-8 or 10-12 repetitions, for three different quadriceps exercises.

Peak torque results indicated no differences in knee torque output between groups ($P = 0.15$ flexion and extension) despite the possibility of AIDS wasting, the loss of lean muscle mass, in the HIV-Seropositive group. The number of repetitions to 50% fatigue decreased across sets regardless of group (Figure 2). The HIV-Seropositive individuals were expected to have lower peak torque values and to perform a lower number of repetitions to fatigue because muscle mass is a major determinant of strength and thus of functional capacity and disability (Roubenoff, McDermott et al. 1999). Therefore, wasting may not have been an issue with the HIV-Seropositive participants in this study.

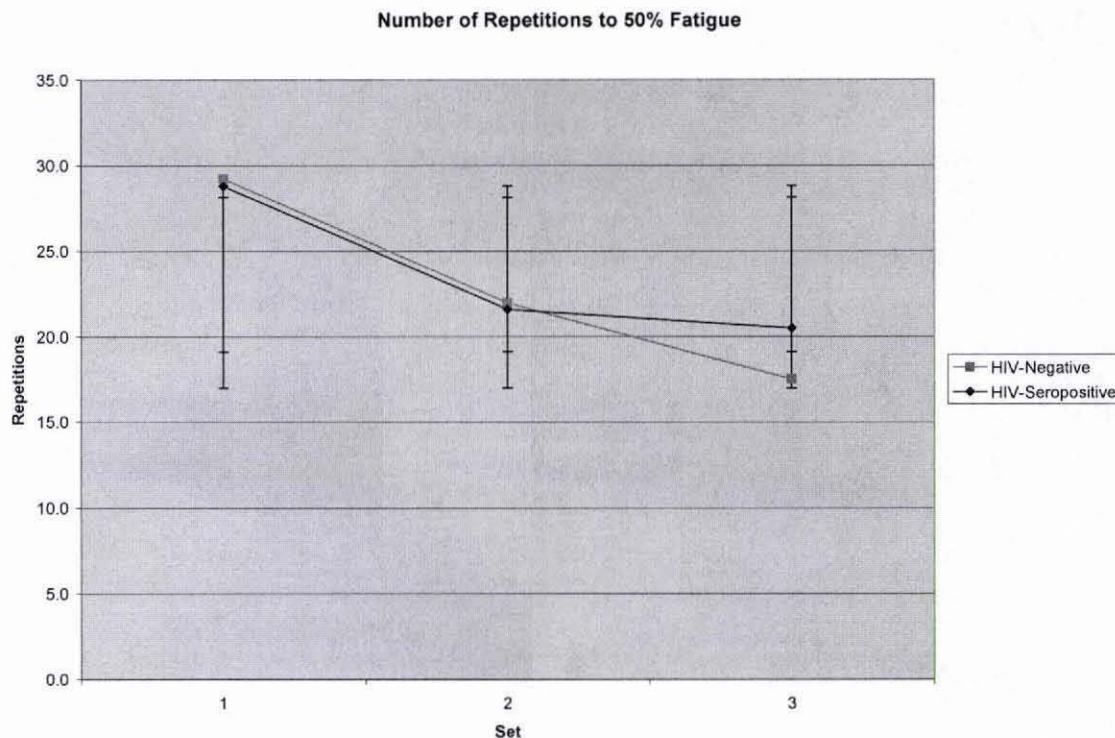


Figure 2. BMI and percent body fat (DEXA) Values (Mean \pm SD)

Body mass index and percent body fat via DEXA indicated that the HIV-Seropositive group had lower body composition values than the HIV-negative group ($P = 0.02$ and $P = 0.01$ respectively). This result may have been due to lipodystrophy among HIV-infected participants (Corless, Kirksey et al. 2005). Lipodystrophy was diagnosed in this study via the examining physician report. The presence of lipodystrophy in five participants did not correlate to CD4 lymphocyte count, antiretroviral duration, or any specific HAART medication. While not statistically significant, all three of the participants taking stavudine were noted to be lipodystrophic.

No significant difference within groups or between groups was seen in CK levels ($P = 0.66$; $P = 0.09$ respectively). However, after further review of the data there appears to be a slight increase in CK levels 24-hours post-exercise regardless of group. This result was revealed to be within normal time limits for peak CK levels seen in previous exercise studies with healthy individuals (Vincent and Vincent 1997; Cleary, Kimura et al. 2002). Results of previous studies indicated that concentric anaerobic exercise did not increase CK levels in healthy individuals. Conversely, significant increases in CK were revealed in eccentric anaerobic exercise of healthy individuals. These results were attributed to higher mechanical tension per unit cross-sectional area in eccentric exercise. (Sargeant and Dolan 1987; Lavender and Nosaka 2006) Also, Gibala et al. (1995) via needle muscle biopsies revealed significantly more disrupted muscle fibers in healthy individuals after eight sets of eight eccentric repetitions than concentric repetitions.

Our lack of significance may have been influenced by the low number of participants in both groups tested ($n=19$), unequal sample size for HIV-Seropositive and HIV-negative groups ($n=13$ and $n=6$ respectively), and large variation for both groups (Appendix H). High standard deviation for CK levels may be attributed to three outliers found in the HIV-Seropositive group and two in the HIV-negative group.

Within the limitations of this study we concluded that a single acute bout of anaerobic concentric resistance exercise did not sufficiently cause a significant increase in CK levels in HIV-Seropositive individuals. Thus, the focus of future

research should involve the effects of single and multiple acute bouts of eccentric and concentric exercise on CK levels in HIV-Seropositive individuals. Since the risk of HIV replication is high, the initial acute bout of exercise should not influence a sudden activation of the immune system, and consequent replication of the HIV virus. The fact that CK levels in the present study did not significantly increase may help build a safer foundation for anaerobic program design of appropriate rigor. Additional research should include identification of the effects of specific and various combination medications on lipodystrophy, BMI, percent body fat, and CK activity.

Part II

Review of Literature

CREATINE PHOSPHOKINASE LEVELS AND EXERCISE

Aerobic Exercise

Sargeant and Dolan (1987) investigated prolonged eccentric and concentric treadmill exercises. Three females and one male participant performed three treadmill exercise tests including a progressive test to determine maximal oxygen uptake, one downhill test, and one uphill test. Tests were separated by two weeks. Dependent variables included plasma Creatine Phosphokinase (CK) and maximal voluntary contraction (MVC). Student t- test results indicated that MVC in uphill walking slightly decreased 24-hours post-exercise and returned to normal by 48-hours, CK levels were not significantly influenced. Results indicated significant decreases in MVC in downhill walking, and increases in plasma CK levels four-hours post-exercise and continued to increase for 24 hours.

Manfredi, Fielding, O'Reilly, Meredith, Lee, and Evans (1991) performed a study to compare changes in skeletal muscle following a high-intensity eccentric exercise protocol to determine if CK activity was a reliable predictor of muscle damage in older males. Participants were 10 sedentary healthy males, five ranging in age from 20 to 30 and five from 59 to 63 years, who lived in a metabolic ward for the duration of the study and followed a standard diet. On day six, participants resisted backward motion on a cycle ergometer in three 15-minute sessions at 80% VO_{2max} ,

with a five-minute rest period between sessions. Muscle biopsies of the vastus lateralis were taken pre and post-exercise, while blood samples were collected pre-exercise and immediately post exercise and on post-exercise days 1, 3, 5, 8, and 10. Two-way Analysis of Variance (ANOVA) results indicated significant CK elevations on post-exercise days 5, 8, and 10, regardless of group. Muscle biopsy results indicated significantly greater muscle damage in the group of older males immediately post-exercise and on post-exercise day 10. The authors concluded that CK was not a sensitive indicator of exercise-induced focal damage.

Totsuka, Nakaji, Suzuki, Sugawara, and Sato (2002) performed a study to investigate the break point of CK release post-daily endurance exercise. Participants included 15 healthy untrained males ages 19-21 years. The exercise protocol consisted of a 60 rpm, 90-minute cycle ergometer test on three consecutive days. Blood samples were collected on day one 30 and 60-minutes after initiation of exercise and then immediately post-exercise and at 1, 3 and 12-hours. On days two and three blood samples were taken pre-exercise and the post-exercise at 1 and 12-hours. Two-way ANOVA with repeated measures results indicated that serum CK levels increased significantly three hours post-exercise on day one and continued to gradually increase through day three.

Summary

Aerobically, an immediate increase in CK was revealed after 90-minutes of cycling on three consecutive days and gradually increased throughout the three day study (Totsuka, Nakaji et al. 2002). Conversely, no differences in CK levels were

indicated between two groups of males who cycled eccentrically in three 15-minute bouts, although significantly higher levels of muscle damage were revealed in the older group of males (Manfredi, Fielding et al. 1991). In treadmill tests, results revealed that eccentric exercise CK levels were significantly higher than concentric exercise levels (Sargeant and Dolan 1987). While, CK is not the best available predictor of muscle damage, it is easy to assess and widely utilized (Hortobagyi and Denahan 1989; Gibala, MacDougall et al. 1995).

Anaerobic Exercise

Tesch, Komi, and Hakkinen (1987) investigated the effects of various types of six-month exercise protocols and three-month detraining periods had on skeletal muscle enzymes that included, CK, hexokinase (HK), myofibrillar ATPase (ATPase), citrate synthase (CS), phosphofructokinase (PFK), lactate dehydrogenase (LDH), and myokinase (MK). Participants were 21 physically active males, accustomed to weight training but noncompetitive, who were divided into three groups: heavy resistance (HR; n=11), explosive strength (EX; n=10) groups, and control group (n=8). The HR group performed back squats using loads of 70-100% 1-repetition maximum (RM) and three to five “super heavy” eccentric repetitions three times per week during months three, five, and six. The EX group performed various squatting exercises focused on improving the rate of force production. With detraining the exercise protocol was stopped but participants were encouraged to continue all other normal activities. Muscle biopsies of the vastus lateralis were taken pre-exercise and

during the exercise at three and six months, as well as post-detraining. Student's t test and ANOVA results indicated HK, ATPase, CS, and PFK activity decreased with training in HR and EX groups. Creatine Phosphokinase significantly decreased after exercise in the HR group and LDH was not affected.

Nosaka and Clarkson (1992) conducted a study to determine if increases in eccentric muscle damage affected post-exercise increases in plasma CK levels. Twenty-two female participants were divided into two groups who performed eccentric forearm flexor exercises using a modified arm curl machine. Each motion lasted three seconds and was repeated every 15 seconds. Group one performed the exercise bilaterally on the same day and group two performed the exercise with one arm and then used the contralateral arm three to five weeks later. Blood samples were collected pre-exercise and immediately post-exercise and on post-exercise day five. Repeated measures ANOVA results indicated delayed increases in CK levels regardless of group. No significant differences between groups or between arms were revealed. The authors concluded that CK increases post-eccentric exercise were not indicative of the degree of muscle damage.

Staron, Hikida, Murray, Nelson, Johnson, and Hagerman (1992) investigated skeletal muscle damage in successive muscle biopsies of strength-trained and untrained individuals. The trained group consisted of 13 males and eight females, the untrained group consisted of seven males and five females. The eight-week training protocol consisted of two warm-up sets followed by three sets to failure of either six to eight or 10-12 repetitions, for three different quadriceps exercises. Muscle biopsies

were taken from the superficial portion of the vastus lateralis pre-exercise, and every two weeks during training. Two-way ANOVA with repeated measures results revealed no differences in CK within groups over time. The highest serum CK levels were found in the trained group after two weeks of high-intensity training.

Karamizrak, Ergen, Tore, and Akgun (1994) performed a study to compare the effects of short-duration high-intensity exercise on enzyme activity of 33 male distance runners and cyclists (age 16-31 years) and 30 male leisure sport athletes (age 17-34 years). Participants performed a five-minute warm-up at 60 rpm with a 1 kp resistance and three 30-second Wingate cycle ergometer tests with a six-minute rest period between tests for the distance athletes and an eight-minute rest period for the leisure athletes. Blood samples were collected pre-test and immediately post-test and again six hours post-test. Student t-test results showed significant blood lactate level increases following the bike tests, regardless of group. Significant increases in CK levels were revealed between pre- and post-tests regardless of group. Additionally, CK levels in the athletic group were significantly higher than the control group.

Gibala, MacDougall, Tarnopolsky, Stauber, and Elorriaga (1995) performed a study to investigate concentric and eccentric exercises and muscle fiber disruption, measured via muscle biopsy. Participants were eight males (means; age 21.8 ± 0.9 yr, height 181.0 ± 5.3 cm, mass 79.8 ± 5.5 kg), who performed one bout of eight sets of eight repetitions at a two-second pace using 80% 1-RM of the elbow flexors on an inclined bench with a dumbbell. One arm was used to perform concentric exercises and the contralateral arm was used to perform eccentric exercises. The arm was

moved passively without weight in the direction not being tested. Electron microscope data ANOVA results indicated a significantly higher proportion of severely disrupted muscle fibers post-exercise in the eccentric exercise arm than in the concentric exercise arm.

Hurley, Redmond, Pratley, Treuth, Rogers, and Goldberg (1995) investigated the effect of a total body heavy resistance strength training program on CK and muscle soreness in older males. Participants were 35 untrained healthy males ranging in age from 50-69 years who were divided into resistance (n=23) and control groups (n=12). The resistance group trained three times per week for 16 weeks with 15 repetitions of eccentric and concentric exercises alternating upper and lower extremities. Blood samples were drawn pre-exercise and at eight, 24, and 48-hours post-initial exercise, then again post-exercise at eight, 24, and 48-hours. Repeated measures 4 x 2 ANOVA results revealed a significant increase in CK activity from baseline to 24-hours post-initial exercise. The 3-RM strength tests pre- and post-exercise protocol revealed an increase in muscle strength. No significant CK activity was revealed until 48-hours post-exercise when CK levels decreased. Eleven of the participants reported no muscle soreness after the initial exercise, while three participants reported levels of soreness between three and seven out of 10. The authors concluded that occasionally CK activity coincided with muscle soreness but not significantly.

Vincent and Vincent (1997) performed a study to investigate the relationship between CK response, soreness, and muscle function after resistance exercise.

Participants were 20 college-aged males, who were divided into untrained (no resistance training for the past three years) and trained (a minimum of three years of weightlifting experience) groups. The exercise protocol consisted of 12-RM knee extension exercises (leg press and leg extension) on day one and 12-RM knee flexion exercises (double and single leg curls) on day two. Blood samples were collected pre-exercise, and on post-exercise days 1, 2, 3, 4, 5, and 10. Repeated measures ANOVA results revealed significant increases in CK levels in untrained individuals when compared to trained individuals. Muscle soreness and CK levels correlated in the untrained, but did not correlate well in the trained participants as they presented with muscle soreness without significant CK increases. The authors concluded that muscle soreness can occur independently of CK level. Significantly higher CK levels were indicated in the untrained group in all blood samples post-exercise. Peak CK values were revealed on post-exercise days four to five.

Hyatt and Clarkson (1998) performed a study to investigate enzyme clearance as a reason for blunted CK response in two eccentric exercise sessions separated by six days. Ten college-age males performed two sets of 50 unilateral maximal eccentric elbow flexor muscle exercises on a modified preacher curl bench at a three to five second cadence with a 10-12 second rest period between sets. Participants were separated into a control group, who performed exercise with the arm used in the first exercise session, and an experimental group, who used the contralateral arm. Blood samples were collected pre-exercise and post-exercise 2, 6, 24, 48, 72, 96, 120-hours after both sessions. Three-way ANOVA results indicated significantly higher

total CK levels in the experimental group when the contralateral arm was used.

Control group total CK levels decreased after the second session.

Dolezal, Potteiger, Jacobsen, and Benedict (2000) conducted a study to investigate CK levels following three bouts of eccentric exercise. Participants were 18 college-age males, who were divided into two groups, nine in a resistance-training group and nine in an untrained group. The exercise protocol consisted of eight sets of 6-RM of eccentric leg press and a three minute rest period between sets performed on three consecutive days. Blood CK levels were measured pre-exercise and post-exercise 24, 48, and 72-hours. Repeated measures 2 x 4 ANOVA results indicated significantly higher CK levels in the untrained group compared to the trained group at 24, 48, and 72-hours post-exercise. Significant increases in CK levels were revealed from baseline to 24-hours post-exercise and peaked 48-hours post-exercise regardless of group. Total CK values decreased from 48 to 72-hours but were still significantly higher than at baseline.

Liu, Chang, Chan, Tsai, Lin, and Hsu (2005) conducted a study to investigate the changes in muscle cell injury and antioxidant capacity of female weightlifters. Participants were 19 female elite weightlifters and 17 age-matched non-athlete females who took part in a six day, two sessions per day, exercise protocol. Each session lasted two to three hours and included a mixture of whole body weightlifting exercises. Blood samples were taken pre-exercise, after a 12-hour fast, post-exercise protocol and again after a two-day rest period. Independent t-test and paired t-test results indicated that CK activity, Vitamin E, and plasma glutathione in professional

weightlifters were significantly higher than that of the control group after a one-week intensive resistance-training regimen.

Lavender and Nosaka (2006) investigated the difference in eccentric and concentric exercises using the elbow flexors. Twelve male participants performed six sets of five repetitions of concentric exercise with one arm and eccentric exercise with the contralateral arm. Concentric dumbbell exercises were performed at a two to three second cadence while eccentric exercises were performed at a three to four second cadence. Resistance consisted of 50% participants' 1-RM. Two-way ANOVA with repeated measures were used to analyze changes in girth, soreness, and CK levels. The results revealed significantly higher values in all dependent variables post-eccentric exercises than post-concentric exercises.

Summary

Anaerobic resistance exercise tests using opposing arms for concentric and eccentric exercises (Gibala, MacDougall et al. 1995; Lavender and Nosaka 2006) results revealed eccentric exercises to have significantly higher CK levels than concentric exercises. Increases in CK levels post-eccentric exercise were found to not be indicative of the degree of muscle damage (Nosaka and Clarkson 1992; Vincent and Vincent 1997). Trained individuals revealed significantly higher CK levels post-exercise than untrained individuals, when performing three Wingate tests with a six-minute rest period between (Karamizrak, Ergen et al. 1994), and in resistance training in professional weightlifters (Liu, Chang et al. 2005).

HIV-SEROPOSITIVE PARTICIPANTS AND EXERCISE

An overview of Lipodystrophy and AIDS Wasting

The treatment for AIDS wasting, the loss of lean muscle mass, and lipodystrophy, the redistribution and loss of subcutaneous body fat, are limited and controversial (Mangili, Murman et al. 2006). One known physiological intervention to increase lean muscle mass is progressive resistance training (PRT). However, immune system activity must be considered when implementing a strenuous PRT program. Short periods of intensive PRT have been shown to be efficacious in increasing strength and lean body mass in HIV-Seropositive adults (Rigsby, Dishman et al. 1992; Roubenoff, McDermott et al. 1999).

Corless Kirksey, Kemppainen, Nicholas, McGibbon, Davis, and Dolan (2005) investigated drug regimen adherence in 165 HIV-Seropositive participants and found that those who were more compliant developed lipodystrophy and other symptoms ultimately resulting in reduced compliance. However, due to the economic status of the participants, the missed doses were thought to be influenced by insurance and forgetfulness. Conversely, lipodystrophy development often detrimentally affects medication adherence. Collins, Burgoyne, Wagner, Abbey, Halman, Nur, and Walmsley (2006) investigated drug regimen adherence in 77 (60 male and 17 female) HIV-Seropositive participants, with at least one lipodystrophy-associated body fat change. Results revealed that participants reporting self-assessed fat redistribution compared to those without alterations were not more likely to miss any doses of medication. Currently, research to investigate treatment of lipodystrophy due to

HAART, include growth hormone and exercise studies (Terry, Sprinz et al. 2006).

The most effective way to ensure that the weight gained during these treatments becomes lean muscle mass is to implicate a PRT program (Roubenoff, McDermott et al. 1999; Roubenoff, Skolnik et al. 1999).

Aerobic Exercise

LaPerriere, Fletcher, Antoni, Klimas, Ironson, McGibbon, Davis, and Dolan (1991) performed a study to investigate the effects of aerobic exercise on an AIDS risk group of 39 males ranging in age from 18 to 40 years who were all HIV-1 asymptomatic. Participants exercised for 45-minutes on a stationary bicycle three times per week for 10 weeks. The protocol consisted of a two-minute warm-up at 70% maximum heart rate (MHR), followed by a series of three-minute bouts of 70-80% MHR, separated by two-minute rest periods. Analysis of variance results indicated increases in aerobic capacity and helper/inducer (CD4) cell count after five weeks. No significant changes in VO_{2max} or control variables (sleep behavior, physical activity, serum concentrations of albumin or hematocrit) were revealed, while depression and anxiety decreased regardless of group. The authors concluded that the 10-week exercise program improved overall health and slowed the progression of the disease in HIV-Seropositive patients.

Rigsby, Dishman, Jackson, Maclean, and Raven (1992) investigated the effect of a 12-week exercise program on HIV-Seropositive participants (n=37). Participants were divided into exercise (n=19) and counseling groups (n=18). The exercise

protocol consisted of 20 minutes on a stationary bike and a resistant exercise program for main muscle groups one hour per day, three times per week. Counseling consisted of group sessions twice a week for two hours, which involved teaching nutrition, exercise and positive thinking. Multivariate analysis of variance (MANOVA) with repeated measures results indicated no significant changes in total leukocytes (LeukC), CD4+, CD8+, and total lymphocyte (LymphC) activity. Significant decreases in heart rate and increases in aerobic capacity and strength were revealed in the exercise group but not in the counseling group.

Nieman, Miller, Henson, Warren, Gusewitch, Johnson, Davis, Butterworth, and Nehlsen-Cannarella (1993) investigated the effects of high and moderate-intensity exercise on natural killer (NK) cells in healthy individuals. Natural killer cells represent a first line of defense against viral infections, such as HIV. Participants included 10 well conditioned male runners who were divided into two groups. The high-intensity group performed a 45-minute treadmill test at 80% VO_{2max} , while the moderate-intensity group performed a 45-minute graded treadmill walk at 50% VO_{2max} . The groups were reversed two weeks post-initial trial to complete a second session. Repeated measures 2 x 5 ANOVA results indicated an increase of post-exercise lymphocytes in the high-intensity group and normal lymphocyte levels one hour post-exercise regardless of groups. Significant increases of NK levels were revealed immediately post-exercise and decreased below pre-exercise levels one hour post-exercise regardless of group.

Mustafa, Sy, Macera, Thompson, Jackson, Selassie, and Dean (1999) performed a study to investigate the effects of a moderate exercise program on the progression of HIV to AIDS. Surveys were collected over several years from 156 HIV-1 Seropositive and 259 HIV-1 negative males in New York City and a control group consisting of HIV-Seropositive males who exercised less than three times per week. Simple linear regression results indicated significant increases in CD4 cell count, significant decreases in risk of progression to AIDS, and significant decreases in risk of death for those that exercised more than three times per week.

Perna, LaPerriere, Klimas, Ironson, Perry, Pavone, Goldstein, Majors, Makemson, Talutto, Schniederman, Fletcher, Meiji, and Koppes (1999) performed a study to investigate the effects of a 12-week aerobic exercise program on early symptomatic HIV-infected individuals. Participants were 18 symptomatic HIV-1 Seropositive and 10 HIV-negative who performed aerobic exercise three times per week with each session lasting 45 minutes at 70-80% MHR for three-minute periods. Repeated measures ANOVA results indicated that compliant exercise participants revealed significant increases CD4 cell count by 13%. Noncompliant participants revealed significant decreases CD4 cell counts 18% while the control group decreased 10%. Significant improvements were revealed with compliant participants in peak oxygen consumption, oxygen pulse, maximal tidal volume, and ventilation.

Roubenoff, Skolnik, Shevitz, Snyderman, Wang, Melanson, and Gorbach (1999) investigated the effects of a single bout of strenuous exercise on plasma HIV ribonucleic acid (RNA). Participants (25 HIV-Seropositive) performed a 15-minute

exercise protocol consisting of stepping up 225 times with the left leg and stepping down 225 times with the right leg. Repeated measures ANOVA results indicated significant increases in CK levels six hours post-exercise with a return to baseline one-week post-exercise. Human Immunodeficiency Virus RNA activity post-exercise results were not significant.

Terry, Sprinz, and Ribeiro (1999) investigated the effect of high-intensity exercise and moderate-intensity aerobic exercise in HIV-infected individuals. Participants were 14 males and 7 females who were divided into moderate-intensity (n=10) and high-intensity (n=11) groups. The exercise protocol consisted of a 12-week aerobic exercise program, three times per week, for one hour each session. Target heart rate for the moderate-intensity group was 55-60% MHR, and 75-85% MHR for the high-intensity group. Two-way ANOVA with repeated measures results indicated no significant changes in peak heart rate, percentage body fat, body mass, or estimated body density. The high-intensity group revealed significant increases in systolic blood pressure and no significant changes were revealed CD4, CD8, leukocyte, or lymphocyte activity at six or 12 weeks. The authors concluded that short-term aerobic exercise programs may be safely prescribed to HIV-Seropositive patients.

Summary

The above research indicated that individuals diagnosed with a chronic disease such as HIV or AIDS can be safely placed on an aerobic exercise program (Terry, Sprinz et al. 1999) that may increase the productivity of the immune system

and help to slow the progression of the disease. Exercise helps to alleviate muscle atrophy, weakness, and fatigue symptoms by improving muscle strength, flexibility, and cardiopulmonary function as well as increase CD4 lymphocyte cell counts (A LaPerriere 1991; Mustafa, Sy et al. 1999). Significant increases in CD4 cell count were found after a 12-week aerobic exercise protocol of 45-minutes per session, three times per week, at 70-80% MHR (LaPerriere, Klimas et al. 1997; Perna, LaPerriere et al. 1999). Under the same conditions aerobic capacity was significantly increased, aiding in the function of daily activity (Rigsby, Dishman et al. 1992; LaPerriere, Klimas et al. 1997; Perna, LaPerriere et al. 1999).

Anaerobic Exercise

Roubenoff, McDermott, Weiss, Suri, Wood, Bloch, and Gorbach (1999) investigated the effect of PRT on HIV-infected individuals. Participants were recruited from a study of 575 HIV-Seropositive males (n=20) and females (n=5) who were followed in six-month intervals to assess disease progression. The PRT protocol consisted of training three times per week for eight weeks using Keiser pneumatic resistance equipment for double leg press, knee extension, seated chest press, and seated row. Resistance was set at 80% 1-RM. Analysis of variance results indicated a significant increase in muscle group strength in males and females, with slightly more strength in males. No significant change in bone mineral content or weight was revealed. Participants who were diagnosed with AIDS wasting revealed significantly higher increases, at eight and 16 weeks, in lean body mass than the

weight-stable individuals. Additionally, the AIDS wasting participants revealed significant increases in fat mass.

Strawford, Barbieri, VanLoan, Parks, Catlin, Barton, Neesem Christiansen, King, and Hellerstein (1999) investigated the effect of resistance exercise and supraphysiologic androgen therapy in males diagnosed with HIV-related weight loss. Participants were 24 HIV-Seropositive males (all given a testosterone enanthate injection) who were divided into placebo and oxandrolone groups, and placed in a metabolic ward for 8 weeks. The exercise protocol involved three, one-hour resistance training sessions, for major muscle groups per week, alternating upper and lower body workouts. Each set consisted of 10 repetitions at 80% 1-RM, with reassessment of weight at week four. Repeated measures ANOVA results indicated significant increases in weight, lean muscle mass, resting energy expenditure, and strength with the oxandrolone group having more significant increases than the placebo group. Significant decreases in fat mass were revealed regardless of group.

Bhasin, Storer, Javanbacht, Berman, Yarasheski, Phillips, Dike, Sinha- Hikim, Shen, Hays, and Beall (2000) investigated testosterone replacement and resistance exercise in HIV-Seropositive males with HIV-related weight loss and low testosterone levels. Participants were 49 HIV-Seropositive males who were divided into no testosterone and no exercise (n=12), testosterone and no exercise (n=15), placebo and exercise (n=11), and testosterone and exercise (n=11) groups. The 16-week exercise protocol involved four weeks of three sets of 12-15 repetitions at 60% 1-RM, six weeks of 90% 1-RM and 70% 1-RM alternately, and six weeks of

increased upper body loads (7%) and lower body loads (12%) for five sets. Analysis of Variance results revealed no significant changes in muscle strength, thigh muscle volume, body weight, and fat-free mass in the placebo alone group. Significant increases in strength, thigh muscle volume, body weight, and significant decreases in fat-free mass were revealed in the testosterone alone and testosterone-exercise groups, and most significantly in the exercise alone group.

Summary

Anaerobically, a six-month, three times per week resistance exercise program using all major muscle groups of the body revealed a reversal of AIDS wasting by increasing muscle mass and strength as well as fat mass (Roubenoff, McDermott et al. 1999). The authors of an androgen injection study concluded that when outside factors are limited, such as nutrition, testosterone replacement and resistance exercise significant increases in muscle size and strength in HIV-Seropositive males with low testosterone levels are seen (Bhasin, Storer et al. 2000) Authors of another androgen injection study concluded that extremely high doses of androgens were not required for beneficial interactions with progressive resistance training in males with HIV-related weight loss (Strawford, Barbieri et al. 1999).

Appendices

Appendix A Data Collection Sheet

Patient ID Number – _____ DOB - _____ Date -

Gender - M F Ethnicity - Hispanic Non-Hispanic

Race - Caucasian African-American Pacific Islander

Asian (Specify) _____ Mixed (Specify) _____

HIV Status Positive Negative Date of Diagnosis _____

CD4 + (Date) _____ Viral Load (Date) _____

Past Medical History/Review of Systems

Current Medications (Include duration)

Stable HAART x 3 months? Yes No

Exclusionary Medications? Yes No

Alcohol Consumption? Yes, Quantify _____ No

Exercise? Yes, Frequency and Type _____ No

PE – Vitals: BP _____ P _____ R _____ T _____ Waist, Hip Circ. _____

Lipodystrophy? Yes No

CV NI Abnl

Pulm NI Abnl

MSK NI Abnl

Neuro NI Abnl

Other NI Abnl

Abnormal Findings:

Appendix B Sample Informed Consent

Study Title: Creatine Phosphokinase Elevations Following Exercise In Individuals Infected With The Human Immunodeficiency Virus

Principal Investigator: Larry Day, M.D.
Le'ahi Hospital, Young Building, 3675 Kilauea Avenue, 5th Floor, Honolulu, HI
96816
(808) 737-2751

INTRODUCTION

You are being asked to take part in a research study. The doctor in charge of this study is Dr. Larry Day. Before you decide if you want to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

Resistance exercise (weight lifting) helps to develop strength which may improve athletic performance and overall fitness. Temporary damage to muscles can occur as the result of resistance training. While overtraining may be harmful to muscle, some muscle damage may be necessary to benefit from resistance exercise. However, the ability to recover from this damage may be impaired in individuals with diseases of the muscle.

Medications used in the treatment of human immunodeficiency virus (HIV) infection may be associated with muscle disease. Symptoms of muscle disease include weakness, muscle soreness, loss of muscle bulk and fatigue. These symptoms can be absent, however, even when muscle disease is present in some people with HIV. This may be seen in early forms of muscle disease, which may progress if unrecognized. One way doctors can check for muscle disease is to measure markers of muscle damage from the blood. These markers may become more evident after a period of resistance exercise.

Creatine phosphokinase (CK) is the most commonly measured marker of muscle damage found in the blood. This compound acts as a fuel for active muscles. In healthy individuals, CK rises after resistance training but quickly normalizes as

muscles are repaired. This pattern is different in people with muscle disease, which can result in higher levels and prolonged release of CK from muscle after exercise.

While abnormalities in CK levels are well described in HIV-infected individuals, the effect of resistance exercise on these levels is unknown. Measurement of CK levels in HIV-infected study participants compared to healthy individuals may provide some insight into how common muscle disease is in those infected with HIV. Additionally, identification of CK abnormalities may provide the basis for a strength training program designed to improve muscle function.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

Screening

After you have read and signed the consent form, you will come to the clinic for a screening visit to make sure that you meet the requirements for joining the study. At this visit, you will have a physical exam. You will be asked about your medical history, including medications you are taking and medications you have taken in the past. You will also be asked about the amount of alcohol you drink.

About 3 teaspoons of blood will be drawn for baseline CK and a few other blood tests. If you are a woman who is able to become pregnant, you will have an extra teaspoon of blood taken or you will give a urine sample for a pregnancy test. If you are infected with HIV, you will also be asked to provide information regarding your last CD4 ("T cell") count and HIV viral load.

Additionally you will be scheduled for body composition analysis by dual x-ray absorptiometry (DEXA), either at the completion of screening or at the time of study entry. This analysis will provide information regarding your bone density as well as your body fat distribution and muscle mass. There will be no charge for the DEXA or any of the blood draws required for the study protocol.

Entry

If you qualify for the study, you will be asked to perform a single session of resistance exercise. This will involve three sets of 8-10 repetitions of knee flexion and extension using a Biodex 3 exercise machine. This machine ensures that equal resistance is present throughout the range of motion for a given exercise. Your session will be supervised by a personal trainer or member of the research team to ensure that the exercise is being performed safely and correctly.

Blood draws will be necessary 24, 48, and 96 hours after the exercise session. These draws can be performed either at Le'ahi Hospital or directly through Diagnostic

Laboratory Services, Inc. Approximately 1 teaspoon of blood will be removed at each draw to measure post-exercise CK values.

Final Study Visit

A final study visit will take place one week after your exercise session. At this visit you will be interviewed and examined by Dr. Day. Additionally you will have a final blood draw for CK. In recognition of the time and inconvenience required for study participation, you will be reimbursed \$40 at the final study visit.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 20 people will take part in this study. Half of these participants will be infected with HIV while the other half will be healthy, uninfected individuals. The HIV status of the study participants will be kept confidential, however. Only Dr. Day and his research assistant will have knowledge of the medical history of those enrolled in the study.

HOW LONG WILL I BE IN THE STUDY?

The study requires a screening visit, a single session of resistance exercise, and a follow up visit one week after completion of the exercise protocol. Additionally, 3 blood draws for CK (approximately 1 teaspoon each) will be required in between completion of the exercise protocol and the final study visit.

WHAT ARE THE RISKS OF THE STUDY?

Risks of Having Blood Drawn

When blood is drawn from a vein there will be some temporary discomfort and/or the minimal risk of local bruising, infection, bleeding or blockage of the vein. Rarely, fainting occurs.

Risks of DEXA

DEXA scans involve a small amount of radiation exposure, roughly equivalent to 1/10 to 1/20 of that experienced during a chest x-ray. This amount of radiation is similar to the background radiation encountered during a transcontinental flight. This imposes a minimal risk to non-pregnant study participants (see ARE THERE RISKS RELATED TO PREGNANCY? below).

Risks of Resistance Exercise

Moderate intensity resistance exercise may result in injury to the joints or muscles of the study participants. More commonly, transient muscle soreness may occur. Additionally physical exertion may elicit symptoms of previously unrecognized heart or lung disease including chest pain, shortness of breath, palpitations (racing heart) or dizziness. To minimize these risks, study participants will undergo a medical evaluation prior to partaking in the protocol. The exercise session will be supervised by the study personnel and will be preceded by appropriate warm-up and stretching to lessen the chance of injury to the joints and muscles. Finally the exercise may be stopped at any time due to participant discomfort or safety concerns, at the discretion of the participant or the study team (see WHAT HAPPENS IF I AM INJURED? below.)

ARE THERE RISKS RELATED TO PREGNACNY?

Pregnant patients will be excluded from the study participation based on the small risk of x-ray exposure to the unborn fetus. If you can become pregnant, you must have a pregnancy test before you enter this study. The test must show that you are not pregnant. If you think you may be pregnant at any time during the study, tell your study staff right away. You will be discontinued from this study if you become pregnant during the study. The study staff will talk to you about your choices.

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation through this institution. You will not be giving up any of your legal rights by signing this consent form. *I understand that if I am injured in the course of this research procedure, I alone may be responsible for the costs of treating my injuries.*

OTHER INFORMATION

For your safety, you must tell the study doctor or nurse about all the medicines you are taking before you start the study and before taking any new medicines while you are on the study. In addition, you must tell the study doctor or nurse before enrolling in any other clinical trials while you are on the study.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

By measuring your blood CK levels, a previously unrecognized muscle disease may be diagnosed. Additionally body composition analysis by DEXA may help to diagnose bone disorders such as osteoporosis (thinning of the bones) and clarify body fat percentage and distribution. The latter two items may serve as the basis for the development of individualized exercise goals to lessen cardiovascular risk and

improve general physical fitness. It is also possible that you may receive no benefit from being in this study. However, information learned from the study may help others who have HIV and/or muscle diseases.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. A code number, which will be stored in a locked file cabinet will be used instead of your name to help protect your confidentiality. Any publication of the study will not use your name or identify you personally.

Your records may be reviewed by the study staff and study monitors, including the University of Hawaii Committee on Human Studies (a committee that ensures that studies are safe).

WHAT ARE MY RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. You will be treated the same no matter what you decided.

We will tell you about the new information from this or other studies that may affect your health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact Dr. Larry Day at (808) 737-2751.

For questions about your rights as a research subject, contact the Committee on Human Studies, the University of Hawaii's Institutional Review Board (which is a group of people who review the research to protect your rights) at 2540 Maile Way, Honolulu, Hawaii 96822. You may phone them at (808) 956-5007.

Study Title: Creatine Phosphokinase Elevations Following Exercise In Individuals Infected With The Human Immunodeficiency Virus

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

**Participant's Name (print)
Date**

Participant's Signature and

**Study Staff Conducting
Consent Discussion (print)**

Study Staff Signature and Date

Appendix C

Explanation of Exercise Protocol

Hello, my name is Andrea Heeter. I am a certified Athletic Trainer and a graduate student here at the University of Hawaii Manoa. First, thank you for your participation in our research. Dr. Larry Day is present today for any medical concerns as I am also trained in emergency care. If you have any questions please feel free to ask at any time.

The machine that you will be on today is called the Biodex system (point to machine). While you are on the machine you will be performing resistance exercises, like the ones you would perform in a weight room. However, this machine is designed to give you resistance in both directions of your leg motion. It will also vary the resistance to the amount of effort you are giving, while taking recordings of the amount of force being produced. The first set we will use for you to gain comfort with the Biodex. Then you will perform three more sets at a quick pace until I tell you to stop. You will have a two minute rest in between each set. If at any time you feel uncomfortable or any pain, please inform us and the study will be discontinued. First, I am going to ask you to please have a seat in the chair. Do you feel comfortable so far? Are the headrest and back comfortably in place? Now I am going to be walking around you finding the proper setting and measurements. You can just relax.

(After set up)

For this first set I want you to begin by getting used to the horn that sounds for go and the full range of motion that you will be asked to perform. Notice the resistance you feel in both directions. After you feel comfortable with the machine I am going to ask you to push and pull even harder noting the added resistance from the machine. Once you understand what you will be asked to do, I will have you stop. Now I need you to kick all the way to the top and pull all the way back to the bottom as hard and as fast as you can, five times. I am going to be looking at the recordings. Do you understand? Ready... Go...

For the next three sets I am going to be pushing you until almost fatigue. I need you to kick as hard and fast as you can while going through the entire range of motion, just like you did for those last five reps. Wait for the horn and keep pushing until I say stop.

Appendix D
Raw Data

PID	AGE	GENDER	RACE	HIV	ARTDUR	AZT	D4T	TDF	ABC	3FTC	DDI	PI	NNRTI	LACTBL	LACT24
HACRP-009-01	40	1	1	1	21	1	0	0	0	1	0	1	0	0.3	2.3
HACRP-009-02	43	1	1	1	51	0	1	0	0	1	0	0	1	1.3	1.8
HACRP-009-03	62	1	1	1	72	1	0	0	0	1	0	1	0	2.6	2.4
HACRP-009-05	39	1	1	1	24	0	1	1	0	0	0	0	1	1.8	1.1
HACRP-009-06	41	1	1	1	12	0	1	1	0	0	0	1	0	1.3	1.1
HACRP-009-07	43	1	1	1	75	1	0	0	0	1	0	1	0	1.4	2.3
HACRP-009-08	34	1	1	1	12	0	0	1	0	0	1	0	1	0.6	1.5
HACRP-009-09	50	2	1	1	63	1	0	0	0	1	0	1	0	1.4	0.9
HACRP-009-10	42	1	4	1	63	1	0	0	1	1	0	1	0	1.4	1.5
HACRP-009-11	54	1	1	1	14	0	0	1	0	1	0	1	0	2.8	3.4
HACRP-009-13	42	2	2	1	13	1	0	0	0	1	0	1	0	1.2	1.5
HACRP-009-16	57	1	1	1	30	1	0	0	0	1	0	0	1	3	3.6
HACRP-009-17	32	1	3	1	30	1	0	0	0	1	0	0	1	0.9	0.6
HACRP-009-04	36	1	1	0										1.7	1.9
HACRP-009-12	43	1	1	0										0.7	0.9
HACRP-009-14	38	1	4	0										1.3	1.2
HACRP-009-15	36	1	5	0										1.5	0.6
HACRP-009-18	44	2	4	0										1.1	<0.3
HACRP-009-19	46	1	4	0										1.6	2.4

PID	CKBL	CK24	CK48	CK96	CK168	Ckmax	TimeMax	TimeNI	AST	ALT	Cr	Bodyfat	Muscle	BMI	WtoH
HACRP-009-01	226	420	473	860	270	860	96	169	25	42	0.7	28	8724	28.2	0.94
HACRP-009-02	239	210	276	217	190	276	48	96	71	102	0.7	29.1	9646	27.8	1.02
HACRP-009-03	120	267	194	135	92	267	24	48	33	35	0.9	35.5	9395	30.6	1.03
HACRP-009-05	62	81	80			81	24	24	32	45	0.8	10.5	6889	20.3	0.93
HACRP-009-06	171	4259	1517	498	97	4257	24	168	94	144	1.1	23.8	8642	23.3	0.93
HACRP-009-07	90	1486	1597	2770	270	1597	48	169	19	20	0.8	33	8240	28.6	0.97
HACRP-009-08	506	460			215	506	0	168	49	47	0.9	24.7	8737	29.4	0.91
HACRP-009-09	55	89	67	69	81	89	24	24	73	89	1.3	19	5603	18	0.91
HACRP-009-10	66	195	118	68	93	195	24	24	45	70	1	13.5	6330	21.5	0.91
HACRP-009-11	494	673	1143	845	430	1143	48	169	36	54	1.1	26.3	8113	25.8	0.95
HACRP-009-13	99	184	171	195	146	195	96	24	22	23	0.9	30.9	6811	22.9	0.77
HACRP-009-16	47	60	42	56	47	60	24	24	31	24	0.8	34.9	7509	26.9	0.97
HACRP-009-17	567	1842	943	323	359	1842	24	169	27	30	0.8	21.5	9745	23.9	0.83
HACRP-009-04	213	908	756	410	234	908	24	169	41	58	0.9	37.5	12498	35.6	0.93
HACRP-009-12	176	121	127	163	117	176	0	24	25	34	1.2	31.6	10287	30.2	1.03
HACRP-009-14	96	627	332	269	107	627	24	168	24	32	1.2	31.2	8921	28	1
HACRP-009-15	122	140	132	789	399	789	96	169	21	29	0.7	32.4	9821	29.6	0.97
HACRP-009-18	136	225	178	132	174	225	24	24	17	15	0.7	42.5	5840	31.7	0.88
HACRP-009-19	135	306	200	161	195	306	24	48	16	22	1.2	30.9	9684	29.1	0.96

PID	LD	CD4	VL	ExtPeak	FlexPk	ExtHalf	FlexHaf	Set1rep	Set2rep	Set3rep
HACRP-009-01	0	595	0	60	40	30	20	23	20	15
HACRP-009-02	1	330	0	90	50	45	25	30	25	22
HACRP-009-03	0	720	0	80	60	40	30	22	21	19
HACRP-009-05	1			60	41	30	20	28	21	23
HACRP-009-06	1		0	110	60	50	30	34	26	18
HACRP-009-07	0	1061	0	60	30	30	15	24	24	22
HACRP-009-08	0	363	0	70	46	35	23	39	38	21
HACRP-009-09	1			62	32	31	16	40	27	26
HACRP-009-10	0	245	0	88	38	44	19	37	23	16
HACRP-009-11	1			132	73	66	36	33	21	19
HACRP-009-13	0	318	0	98	56	49	28	22	19	19
HACRP-009-16	0	560	0	162	114	81	57	23	18	16
HACRP-009-17	0	567	0	168	64	84	32	33	17	13
HACRP-009-04				120	80	60	40	35	27	23
HACRP-009-12				170	84	85	42	22	26	23
HACRP-009-14		319	0	170	90	85	45	23	16	8
HACRP-009-15				80	46	40	23	33	28	21
HACRP-009-18				74	46	36	23	20	18	17
HACRP-009-19				134	75	67	37	17	12	10

Appendix E
ANOVA Table for Creatine Phosphokinase Blood Collection Time Test
Variable

Source	DF	Type III SS	Mean Square	F-Value	P-Value	G-G P-Value	H-F P-Value
Time	4	2300912.84	575228.21	2.14	0.0867	0.1436	0.1338
Time*Group	4	643399.90	160849.97	0.06	0.6649	0.5324	0.5594
Error(time)	60	16117058.43	268617.64				

Appendix F
ANOVA Table for Isokinetic Test Variables

Appendix F-1 ANOVA Table for Average Number of Repetitions Per Set

Source	DF	Type III SS	Mean Square	F-Value	P-Value	G-G P-Value	H-F P-Value
Time	2	721.51	360.76	24.57	<.0001	<.0001	<.0001
Time*Group	2	21.79	10.89	0.74	0.48	0.46	0.47
Error(time)	34	499.22	14.68				

Appendix F-2 ANOVA Table for Average Peak Torque Knee Flexion

Source	DF	SS	Mean Square	F-Value	P-Value
Model	1	1052.63	1052.63	2.30	0.15
Error	17	7770.53	457.09		
Corrected Total	18	8823.16			

Appendix F-3 ANOVA Table for Average Peak Torque Knee Extension

Source	DF	SS	Mean Square	F-Value	P-Value
Model	1	3520.01	3520.01	2.31	0.15
Error	17	25888.41	1522.85		
Corrected Total	18	29408.42			

Appendix G
ANOVA Table for Body Composition Test Variables

Appendix G-1 ANOVA Table for Average BMI

Source	DF	SS	Mean Square	F-Value	P-Value
Model	1	125.58	125.58	9.98	0.01
Error	17	213.81	12.58		
Corrected Total	18	339.39			

Appendix G-2 ANOVA Table for Average Percent Body Fat (DEXA)

Source	DF	SS	Mean Square	F-Value	P-Value
Model	1	326.02	326.02	6.65	0.02
Error	17	833.89	49.05		
Corrected Total	18	1159.91			

Appendix H
CK Levels in HIV-Seropositive and HIV-Negative (Mean \pm SD)

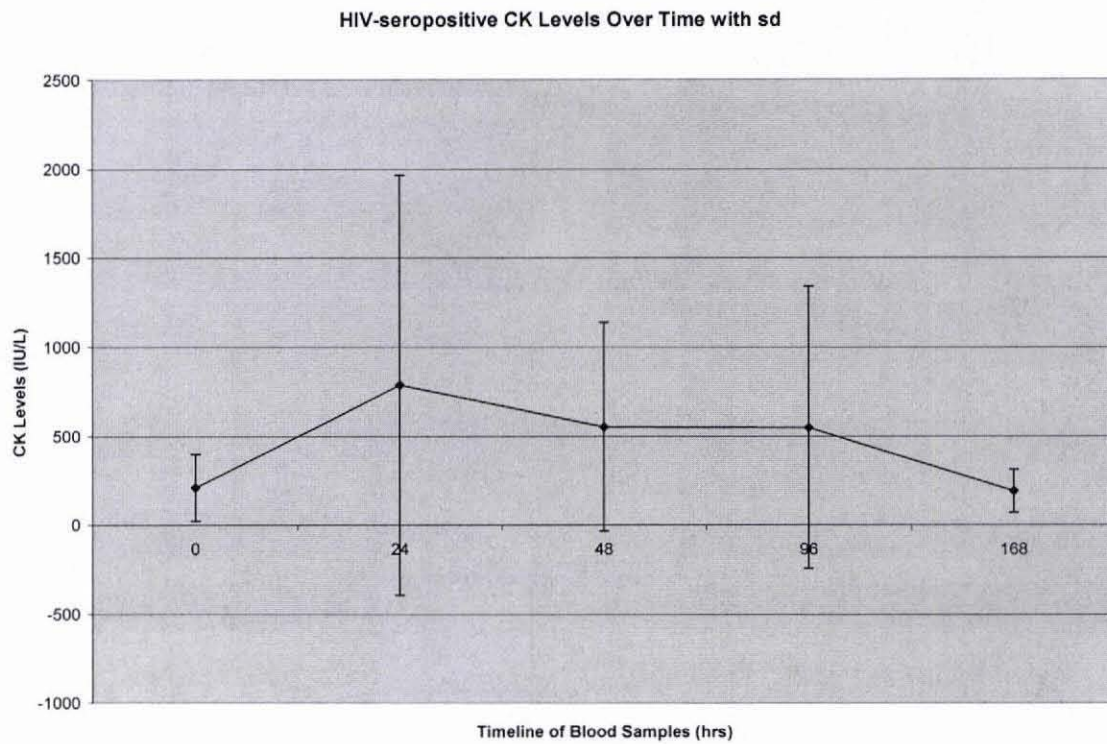


Figure 3. CK Level Activity Over Time Values HIV-Seropositive (Mean \pm SD)

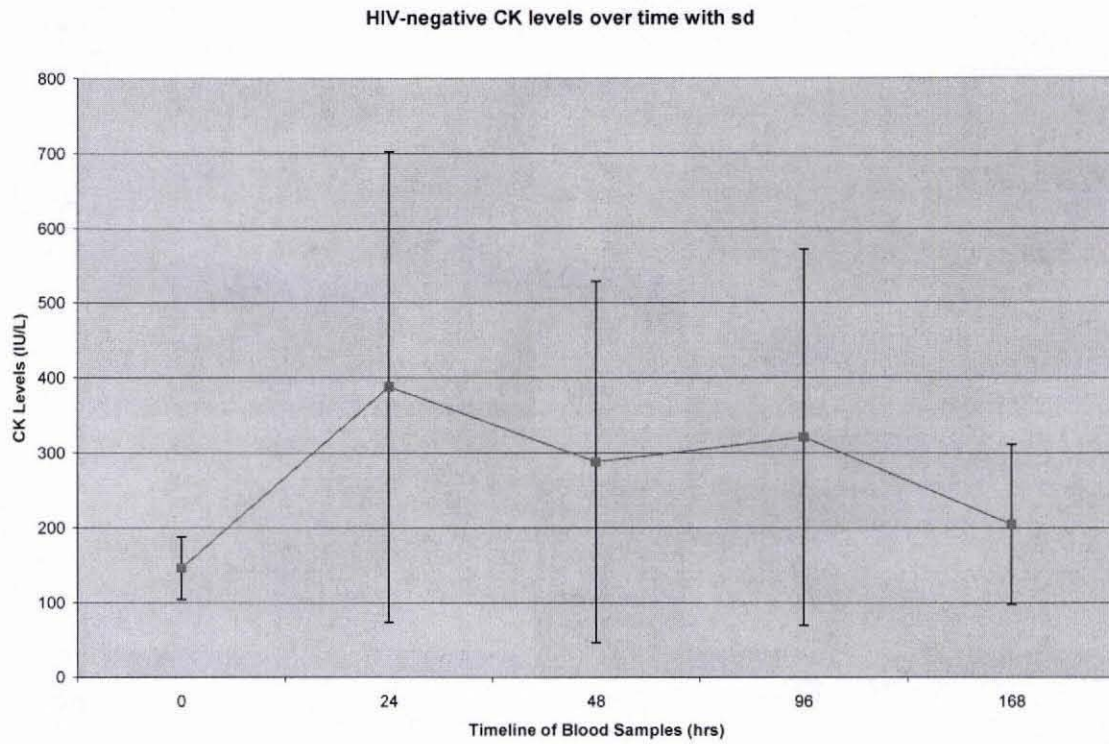


Figure 4. CK Level Activity Over Time Values HIV-Negative (Mean \pm SD)

References

- A LaPerriere, M. A. F., M.H. Antoni, N.G. Klimas, G. Ironson, N. Schneiderman (1991). "Aerobic Exercise Training in an AIDS Risk Group." International Journal of Sports Medicine 12: S53-S57.
- Authier, F. J., P. Chariot, et al. (2005). "Skeletal muscle involvement in human immunodeficiency virus (HIV)-infected patients in the era of highly active antiretroviral therapy (HAART)." Muscle Nerve 32(3): 247-60.
- Bhasin, S., T. W. Storer, et al. (2000). "Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels." Jama 283(6): 763-70.
- Chariot, P. and R. Gherardi (1995). "Myopathy and HIV infection." Rheumatology 7: 497-502.
- Chariot, P. and R. Gherardi (1995). "Myopathy and HIV infection." Curr Opin Rheumatol 7(6): 497-502.
- Cleary, M. A., I. F. Kimura, et al. (2002). "Temporal Pattern of the Repeated Bout Effect of Eccentric Exercise on Delayed-Onset Muscle Soreness." J Athl Train 37(1): 32-36.
- Corless, I. B., K. M. Kirksey, et al. (2005). "Lipodystrophy-associated symptoms and medication adherence in HIV/AIDS." AIDS Patient Care STDS 19(9): 577-86.
- Dalakas, M. C., I. Illa, et al. (1990). "Mitochondrial myopathy caused by long-term zidovudine therapy." N Engl J Med 322(16): 1098-105.
- Dolezal, B. A., J. A. Potteiger, et al. (2000). "Muscle damage and resting metabolic rate after acute resistance exercise with an eccentric overload." Med Sci Sports Exerc 32(7): 1202-7.
- Ercan, A. and S. H. Grossman (2003). "Proteolytic susceptibility of creatine kinase isozymes and arginine kinase." Biochem Biophys Res Commun 306(4): 1014-8.
- Evans, W. J., R. Roubenoff, et al. (1998). "Exercise and the treatment of wasting: aging and human immunodeficiency virus infection." Semin Oncol 25(2 Suppl 6): 112-22.
- Genton, L., D. Hans, et al. (2002). "Dual-energy X-ray absorptiometry and body composition: differences between devices and comparison with reference methods." Nutrition 18(1): 66-70.
- Gibala, M. J., J. D. MacDougall, et al. (1995). "Changes in human skeletal muscle ultrastructure and force production after acute resistance exercise." J Appl Physiol 78(2): 702-8.
- Hortobagyi, T. and T. Denahan (1989). "Variability in creatine kinase: methodological, exercise, and clinically related factors." Int J Sports Med 10(2): 69-80.
- Hurley, B. F., R. A. Redmond, et al. (1995). "Effects of strength training on muscle hypertrophy and muscle cell disruption in older men." Int J Sports Med 16(6): 378-84.

- Hyatt, J. P. and P. M. Clarkson (1998). "Creatine kinase release and clearance using MM variants following repeated bouts of eccentric exercise." Med Sci Sports Exerc **30**(7): 1059-65.
- Jones, S. P., D. A. Doran, et al. (2001). "Short-term exercise training improves body composition and hyperlipidaemia in HIV-positive individuals with lipodystrophy." Aids **15**(15): 2049-51.
- Karamizrak, S. O., E. Ergen, et al. (1994). "Changes in serum creatine kinase, lactate dehydrogenase and aldolase activities following supramaximal exercise in athletes." J Sports Med Phys Fitness **34**(2): 141-6.
- LaPerriere, A., M. A. Fletcher, et al. (1991). "Aerobic exercise training in an AIDS risk group." Int J Sports Med **12** Suppl 1: S53-7.
- LaPerriere, A., N. Klimas, et al. (1997). "Change in CD4+ cell enumeration following aerobic exercise training in HIV-1 disease: possible mechanisms and practical applications." Int J Sports Med **18** Suppl 1: S56-61.
- Lavender, A. P. and K. Nosaka (2006). "Changes in fluctuation of isometric force following eccentric and concentric exercise of the elbow flexors." Eur J Appl Physiol **96**(3): 235-40.
- Lawless, D., C. G. Jackson, et al. (1995). "Exercise and human immunodeficiency virus (HIV-1) infection." Sports Med **19**(4): 235-9.
- Liu, J. F., W. Y. Chang, et al. (2005). "Blood Lipid Peroxides and Muscle Damage Increased following Intensive Resistance Training of Female Weightlifters." Ann N Y Acad Sci **1042**: 255-61.
- Manfredi, R., R. Motta, et al. (2002). "A prospective case-control survey of laboratory markers of skeletal muscle damage during HIV disease and antiretroviral therapy." Aids **16**(14): 1969-71.
- Manfredi, T. G., R. A. Fielding, et al. (1991). "Plasma creatine kinase activity and exercise-induced muscle damage in older men." Med Sci Sports Exerc **23**(9): 1028-34.
- Mangili, A., D. H. Murman, et al. (2006). "Nutrition and HIV infection: review of weight loss and wasting in the era of highly active antiretroviral therapy from the nutrition for healthy living cohort." Clin Infect Dis **42**(6): 836-42.
- Manji, H., M. J. Harrison, et al. (1993). "Muscle disease, HIV and zidovudine: the spectrum of muscle disease in HIV-infected individuals treated with zidovudine." J Neurol **240**(8): 479-88.
- McDermott, A. Y., A. Shevitz, et al. (2001). "Effect of highly active antiretroviral therapy on fat, lean, and bone mass in HIV-seropositive men and women." Am J Clin Nutr **74**(5): 679-86.
- Mustafa, T., F. S. Sy, et al. (1999). "Association between exercise and HIV disease progression in a cohort of homosexual men." Ann Epidemiol **9**(2): 127-31.
- Nieman, D. C., A. R. Miller, et al. (1993). "Effects of high- vs moderate-intensity exercise on natural killer cell activity." Med Sci Sports Exerc **25**(10): 1126-34.
- Nixon, S., K. O'Brien, et al. (2005). "Aerobic exercise interventions for adults living with HIV/AIDS." Cochrane Database Syst Rev(2): CD001796.

- Nosaka, K. and P. M. Clarkson (1992). "Relationship between post-exercise plasma CK elevation and muscle mass involved in the exercise." Int J Sports Med **13**(6): 471-5.
- O'Brien, K., S. Nixon, et al. (2004). "Effectiveness of aerobic exercise in adults living with HIV/AIDS: systematic review." Med Sci Sports Exerc **36**(10): 1659-66.
- Perna, F. M., A. LaPerriere, et al. (1999). "Cardiopulmonary and CD4 cell changes in response to exercise training in early symptomatic HIV infection." Med Sci Sports Exerc **31**(7): 973-9.
- Pietrobelli, A., Z. Wang, et al. (1998). "Techniques used in measuring human body composition." Curr Opin Clin Nutr Metab Care **1**(5): 439-48.
- Polsky, B., D. Kotler, et al. (2001). "HIV-associated wasting in the HAART era: guidelines for assessment, diagnosis, and treatment." AIDS Patient Care STDS **15**(8): 411-23.
- Prou, E., A. Guevel, et al. (1999). "Exercise-induced muscle damage: absence of adaptive effect after a single session of eccentric isokinetic heavy resistance exercise." J Sports Med Phys Fitness **39**(3): 226-32.
- Rigsby, L. W., R. K. Dishman, et al. (1992). "Effects of exercise training on men seropositive for the human immunodeficiency virus-1." Med Sci Sports Exerc **24**(1): 6-12.
- Roubenoff, R., A. McDermott, et al. (1999). "Short-term progressive resistance training increases strength and lean body mass in adults infected with human immunodeficiency virus." Aids **13**(2): 231-9.
- Roubenoff, R., P. R. Skolnik, et al. (1999). "Effect of a single bout of acute exercise on plasma human immunodeficiency virus RNA levels." J Appl Physiol **86**(4): 1197-201.
- Sargeant, A. J. and P. Dolan (1987). "Human muscle function following prolonged eccentric exercise." Eur J Appl Physiol Occup Physiol **56**(6): 704-11.
- Scevola, D., A. Di Matteo, et al. (2003). "Effect of exercise and strength training on cardiovascular status in HIV-infected patients receiving highly active antiretroviral therapy." Aids **17** Suppl 1: S123-9.
- Schwane, J. A., R. T. Buckley, et al. (2000). "Plasma creatine kinase responses of 18- to 30-yr-old African-American men to eccentric exercise." Med Sci Sports Exerc **32**(2): 370-8.
- Shephard, R. J. (1998). "Exercise, immune function and HIV infection." J Sports Med Phys Fitness **38**(2): 101-10.
- Simpson, D. M., K. A. Citak, et al. (1993). "Myopathies associated with human immunodeficiency virus and zidovudine: can their effects be distinguished?" Neurology **43**(5): 971-6.
- Simpson, D. M., D. A. Katzenstein, et al. (1998). "Neuromuscular function in HIV infection: analysis of a placebo-controlled combination antiretroviral trial. AIDS Clinical Group 175/801 Study Team." Aids **12**(18): 2425-32.
- Staron, R. S., R. S. Hikida, et al. (1992). "Assessment of skeletal muscle damage in successive biopsies from strength-trained and untrained men and women." Eur J Appl Physiol Occup Physiol **65**(3): 258-64.

- Strawford, A., T. Barbieri, et al. (1999). "Resistance exercise and supraphysiologic androgen therapy in eugonadal men with HIV-related weight loss: a randomized controlled trial." Jama **281**(14): 1282-90.
- Stupka, N., M. A. Tarnopolsky, et al. (2001). "Cellular adaptation to repeated eccentric exercise-induced muscle damage." J Appl Physiol **91**(4): 1669-78.
- Terry, L., E. Sprinz, et al. (1999). "Moderate and high intensity exercise training in HIV-1 seropositive individuals: a randomized trial." Int J Sports Med **20**(2): 142-6.
- Terry, L., E. Sprinz, et al. (2006). "Exercise training in HIV-1-infected individuals with dyslipidemia and lipodystrophy." Med Sci Sports Exerc **38**(3): 411-7.
- Tesch, P. A., P. V. Komi, et al. (1987). "Enzymatic adaptations consequent to long-term strength training." Int J Sports Med **8 Suppl 1**: 66-9.
- Totsuka, M., S. Nakaji, et al. (2002). "Break point of serum creatine kinase release after endurance exercise." J Appl Physiol **93**(4): 1280-6.
- Vincent, H. K. and K. R. Vincent (1997). "The effect of training status on the serum creatine kinase response, soreness and muscle function following resistance exercise." Int J Sports Med **18**(6): 431-7.