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Review

Physiological and Psychological Effects of Exercise Interventions in HIV Disease

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ABSTRACT

The use of both aerobic and resistance exercise has been shown to improve physiologic parameters such as strength, endurance, time to fatigue, and body composition in the HIV-infected population. Exercise has also been used successfully to treat psychologic conditions such as depression and anxiety that are common in HIV-infected individuals. However, the effects of exercise on immune function in these individuals are uncertain because of conflicting results found among studies. Additionally, many ventures into this area have been attempted with poor research design, resulting in inconclusive evidence or poor generalizability. The focus of this paper is to review the research that has been performed using exercise as an intervention for HIV-infected persons and to determine what needs to be done next to further our understanding of how the HIV-infected body and mind respond to exercise training.

INTRODUCTION

THE COMPLICATIONS resulting from HIV/AIDS radically alter the physiologic and psychological well-being of HIV-infected individuals. Treatment with highly active antiretroviral therapy (HAART) allows HIV-infected individuals to live longer, healthier, and more productive lives than was possible at the beginning of the HIV/AIDS pandemic. However, these life-extending antiretroviral medications often cause side effects that may adversely affect quality of life. Medical researchers are continually seeking more effective methods to treat infected individuals; a vaccine that effectively prevents HIV infection is the ultimate goal.

Health care providers are beginning to prescribe nonpharmacologic complementary and alternative therapies to prevent and manage complications associated with HIV/AIDS. An intriguing, nonpharmacologic treatment for preventing and managing complications of HIV infection is moderate intensity exercise training.[1–3] Moderate-intensity exercise training has been shown not only to be safe, but also beneficial for increasing lean muscle mass, decreasing fat mass, and improving muscular strength. Additionally, exercise has been shown

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to improve various mental health problems in noninfected individuals, thus exercise is being proposed to improve psychological parameters in HIV-infected individuals.[4,5] The purpose of this paper is to identify physiologic and psychological alterations that result from HIV/AIDS and to analyze what is known regarding the effectiveness of exercise interventions in preventing and managing these complications.

A literature search was conducted on the MEDLINE database, with limits set for only original data, using combinations of the keywords "exercise," "HIV," "AIDS," and "physical activity." This search produced 29 research studies involving the use of exercise as an intervention for HIV-infected persons. Searching without limits also produced 12 review articles on this subject, as well as literature regarding the functional limitations of HIV-infected individuals.

Physiologic alterations of HIV infection

HIV-infected persons face many metabolic conditions that researchers have addressed with therapeutic exercise. One such condition, wasting syndrome, is recognized by involuntary weight loss of more than 10% baseline body weight in addition to prolonged fever, chronic weakness, and chronic diarrhea.[6] The significant loss of tissue present with the wasting syndrome increases the risk of mortality and secondary infection.[6]

Lipodystrophy syndrome, a side effect of HAART, is characterized by fat accumulation in the abdomen and trunk with fat loss in the legs, arms, and face.[7,8] HAART can increase the rate of lipid breakdown while decreasing the rate of lipid synthesis, especially in the periphery.[9] Furthermore, the elevation of circulating cytokine levels, such as tumor necrosis factor (TNF)-α, that accompany HIV infection can decrease lipoprotein lipase levels resulting in a decrease in fat deposition.[9]

Immune response to chronic fever and infection results in an elevation of circulating cytokines such as interleukin-1 (IL-1) and TNF-α. Elevated levels of IL-1 and TNF-α can increase resting energy expenditure, and TNF-α has additionally been associated with decreased lipoprotein lipase activity, depletion of energy stores, and suppression of food intake.[10] Increased circulating cytokines further influence metabolic rates by activating the hypothalamic-pituitary-adrenal axis (HPAA), which leads to an increase in glucocorticoid levels. Increased glucocorticoid levels have a catabolic influence on skeletal muscle by slowing protein synthesis rate and increasing protein degradation.[11]

Increased rate of protein turnover and elevated metabolic rate caused by the combined cytokine and glucocorticoid response can increase resting metabolic rates and lead to accelerated depletion of energy stores. During periods of infection, when cytokine and glucocorticoid levels rise significantly, resting energy levels are further elevated and food intake drops, thus causing accelerated and episodic weight loss.[12–14]

HIV-infected individuals also suffer from a high prevalence of anemia, with reports of up to 28% prevalence.[15] The increase in circulating cytokines common with HIV-infection can inhibit the production of erythropoietin (EPO), which may partly explain the low EPO levels reported in HIV-infected individuals.[16] Additionally, certain medications used in the treatment of HIV infection, including zidovudine and trimethoprim-sulphamethoxazole, have been linked to development of anemia.[17]

Psychological alterations of HIV infection

HIV-infected populations have higher incidences of psychiatric disorders than the uninfected population.[18] The most notable psychological abnormalities include anxiety and depression. Heckman and colleagues[19] found that 25% of people age 50 or older living with HIV presented with moderate to severe levels of depression. This is consistent with the 22% to 45% prevalence rate of depression in HIV-infected persons as reported by Penzak and others,[20] who also link depression to altered course of infection due to impaired immune function and nonadherence to therapy.

Depressed and anxious HIV-infected individuals present with decreased natural killer cell activity, increased viral load, and elevated $CD8^+$ T lymphocytes.[21] With the exception of viral load levels, these are the typical immune disorders associated with chronic stress.[22] Sup-

pression of immune function can be traced to hypoactivity of glucocorticoid receptors on immune cells and in limbic regions of the brain. This in turn may lead to increased secretion of proinflammatory cytokines and augmented HPAA activity.[23] Thus, management of stress is significant in treating the HIV-infected population, as increased levels of stress and depression have been associated with more rapid progression to AIDS.[24]

Mental health problems are also important to disease progression because of their negative effect on drug adherence. It has been found that HIV-infected individuals suffering from mental health disorders, regardless of the severity, have poorer drug adherence.[25,26] Specifically, depression has been directly linked to nonadherence in HIV-infected persons.[27–29] Nonadherence to therapy is a major concern because nonadherence leads to faster disease progression and to antiviral-resistant strains of HIV.[30–34]

Aerobic training

The classification of aerobic as a method of exercise refers to exercise that requires oxygen to generate adenosine triphosphate (ATP) for the functioning of skeletal muscle.[35] Aerobic metabolism of lipids occurs in the muscle mitochondria during β-oxidation, which involves energy production from plasma free fatty acids and intramuscular triglycerides. The β-oxidation cycle then feeds acetyl-CoA into the tricarboxcyclic acid (TCA) cycle, also located in the mitochondria, where carbon dioxide (CO_2) and hydrogen (H^+) ions are removed. The H^+ ions are then passed down the electron transport chain where they are oxidized to produce ATP. Additionally, glycolysis via the catabolism of blood glucose and/or muscle glycogen can directly produce energy for the active muscle, as well as producing pyruvate which eventually reaches the TCA cycle in the form of acetyl-CoA.[36] Exercise at a level of 3–6 METs (1 MET = the amount of energy expended during 1 minute of rest) or 50%–85% maximal oxygen uptake ($V_{O_2}max$), for 20 to 60 minutes, is generally prescribed to elicit aerobic conditioning.[37] Other methods of prescription involve training in a target heart rate zone, but because of the occurrence of cardiac neuropathy in HIV-infected persons,[38] this prescription can be unreliable.

Current work to date in the prescription of aerobic exercise for HIV-infected persons has used stationary cycling and treadmill walking as modes of conditioning. Typical prescription has included work at 50%–85% $V_{O_2}max$ or 60%–85% maximum heart rate, 3 times per week for a duration ranging from 10–24 weeks.

Resistance training

Resistance training, or the overloading of skeletal muscle, serves to increase muscular strength and muscular endurance. These functional improvements are possible because skeletal muscle adapts to load by increasing in size, strengthening connective tissue, and improving bone density.[35] Thus, muscle is better able to perform when a stress is again introduced, and functional performance is enhanced. It should be noted, that adaptation of muscle is specific to the type of training performed. In the reviewed literature progressive resistance training has also been used as a means of improving muscular strength and endurance. This type of programming aims at ensuring the appropriate training intensity by continually increasing resistance as the muscle adapts to the implemented load.[37]

Most resistance training is of short duration, less than 60 seconds, thus anaerobic means of ATP production are sufficient. Anaerobic energy production can be carried out by glycolysis, with lactic acid as the byproduct instead of pyruvate. The creatine phosphate (CP) system, in which adenosine diphosphate (ADP) and CP together synthesize ATP, is also a method of anaerobic ATP production.[36]

The reviewed work that has used resistance training as an intervention for HIV infected populations shows a common type of program; 3 sessions per week for 8 weeks consisting of 3 sets of 8 repetitions on each exercise. Proper resistance is based on a 1-repetition maximum (1-RM), preintervention effort on each exercise. Other programs implement a progressive model in which the number of repetition and sets remains constant, while the intensity of the exercise is increased at predetermined time points.

Additional studies have combined aerobic and resistance exercise into the same intervention. These programs usually last 12–16 weeks, and include 20 minutes of aerobic activity followed by 35 to 40 minutes of resistance training. Total workout time has usually been limited to 1 to 1.5 hours and stretching has periodically been included.

RESULTS

The immunologic and physiologic and psychologic effects of exercise are summarized in Tables 1–3.

Physiologic and physiological effects of exercise

Exercise is known to produce many desirable health benefits in apparently healthy populations. Studies have shown that regular exercise reduces the risk of adult onset diabetes,[39] hypertension,[40] and coronary artery disease.[41] Exercise is also beneficial to those with cancer and arthritis, conditions that include wasting.[42–44] Exercise has been shown to positively alter enzymatic activity and increase contractile protein mass, both effects that aid in combating wasting.[45,46]

The literature regarding the effects of exercise on immune function, however, is ambiguous. The primary reason for this lack of cohesion is because of the various methods of data collection that make comparing results nearly impossible. The type of exercise prescribed, whether it is aerobic or resistance, as well as the intensity of the exercise (light, moderate, heavy) is also a factor that makes determining the overall effect of exercise on immune function difficult. Finally, it is absolutely necessary to determine the criteria by which immune function is measured, and whether that measure has any observable health consequence.

With this in mind, however, much information regarding the effects of exercise on immune function have been discovered. After exercise, there is a biphasic response of the immune system in which circulating monocytes and lymphocytes decrease below resting levels,[47–49] while a rise in neutrophils is observed, even hours after exercise.[50–53] A redistribution of lymphocytes occurs in which helper T cells are decreased and natural killer (NK) cell numbers are elevated,[49,54] and the ratio of T-helper to T-suppressor cells can decrease by half.[55,56]

Functioning of these immune components during and after exercise has been addressed. Exercising within the American College of Sports Medicine Guidelines (ACSM), 50%–85% V_{O_2}max, will cause a transient decrease in T-lymphocyte proliferation,[50,54,55,57] although no studies have shown this as being detrimental to health. Research has also not shown exercise to alter the functioning of B-lymphocytes or immunoglobulin production in any way. What is clear, however, is that exercise of less than 60 minutes in duration will cause a dose-dependent increase in NK cell function during and immediately postexercise, but NK cell activity can then be depressed for up to 180 minutes.[58–60]

Regular exercise can also be beneficial to psychological functioning.[61] The use of aerobic exercise has been shown to reduce the severity of depressive symptoms and improve mood.[62,63] Both aerobic and resistance exercise were also found to decrease levels of anxiety over an 8-week period.[64]

Efficacy of exercise in HIV-infected persons

Calabrese and LaPerriere[65] found that exercise is safe and beneficial for HIV-infected persons. To be most beneficial, they recommend beginning exercise before symptoms present and also cite the potential of exercise to provide behavioral benefits. It has even been shown that exercise after periods of acute infection is safe and beneficial for regaining weight lost during the symptomatic period.[2]

While HIV-infected persons are encouraged to participate in exercise, certain limitations do exist. Many of these limitations are the result of loss of lean body mass, decreased muscular strength, or various metabolic changes that are side effects of HAART.[66] A common deficiency directly affecting normal daily activities is maximal oxygen consumption, V_{O_2}max (mL/kg/min), a measure of functional capacity, which was found to be "well below average" in adolescents seropositive for the HIV virus compared to age-matched, uninfected controls.[67]

TABLE 1. IMMUNOLOGIC OUTCOMES OF EXERCISE INTERVENTIONS IN HIV-INFECTION POPULATIONS

Author	*Subjects*	*Number*	*Intervention*	*Results*
LaPerriere et al., 1990	Males	Total 23: Exercise (n = 10) Control (n = 13)	45-minutes of aerobic exercise on a stationary bicycle at 80% age predicted max HR	Control: 61 cells/mm^3 decrease in $CD4^+$ count Exercise: 38 cells/mm^3 increase in $CD4^+$ count
LaPerriere et al., 1991	Males, 18–40 yrs old	Total 39: HIV + exercise (n = 12) HIV + controls (n = 10) HIV-exercise (n = 11) HIV-controls (n = 6)	5 weeks of interval training on stationary bicycle at 70–80% max HR, 3 times per week for 45 minutes a session	Significant increase in exercise group $CD4^+$ cells (904 vs. 1020 mm^3) $CD45RA^+CD4^+$ (no quantification given)
MacArthur et al., 1993	Males and females, 21–46 yrs old	Total 32: Females (n = 2) 10 completed 12 wks, 6 completed 24 wks	24 weeks of cardiovascular exercise at 50–60% V_{O_2} max for low-intensity group and 75–85% V_{O_2} max for high-intensity group, 3 times a week with a caloric expenditure of 250, 350, and 500 k/cal per session for weeks 1–8, 9–16, and 17–24, respectively	Week 12: No significant change in $CD4^+$ cells (170* μL vs. 190* μL) Week 24: No significant change in $CD4^+$ cells (185* μL vs. 195* μL)
LaPerriere et al., 1994	Males, 18–40 yrs old	Total 14: Exercise (n = 7) Control (n = 7)	10 weeks of training on stationary bicycle at 70–80% max HR, 3 times per week for 45 minutes per session	Significant increases in: $CD2^+$ (1717 vs. 2183 mm^3) $CD4^+$ (942 vs. 1280 mm^3) $CD8^+$ (655 vs. 816 mm^3) $CD45RA^+CD4^+$ (312 vs. 955 mm^3) $CD20^+$ (162 vs. 244 mm^3)
Stringer et al., 1998	Males and females, 27–45 yrs old	Total 26: Females (n = 3) Control (n = 8) Moderate (n = 9) Heavy (n = 9)	6 weeks of training on stationary bicycle at an increasing work rate from 15–25 W/min until exhaustion, with time adjusted so each group produced the same work, 3 times per week	Moderate: No significant changes in $CD4^+$ count (297 vs. 310 mm^3) Moderate: No significant change in viral load (56,101 vs. 45,698/mL) Heavy: No significant changes in $CD4^+$ count (342 vs. 339 mm^3) Heavy: No significant change in viral load (11,706 vs. 10,326/mL)
Terry et al., 1999	Males and females, 23–39 yrs old	Total 21: Females (n = 17) High intensity (n = 11) Moderate intensity (n = 10)	12 weeks of treadmill training at 60% max HR (moderate) or 84% max HR (high) 3 times a week for 30 minutes	No significant changes from baseline at 6 or 12 weeks for: $CD4^+$ cells (592 vs. 614 vs. 683 mm^3) $CD8^+$ cells (1030 vs. 1242 vs. 1252 mm^3) Leukocytes (6344 vs. 6400 vs. 6930 mm^3) Lymphocytes (2148 vs. 2627 vs. 2638 mm^3)
Mustafa et al., 1999	Males	Total 156	Self-report of exercise 3–4 times per week considered exercise and less being nonexercisers	Exercise group showed slower progression to AIDS and slower progression to death from AIDS as well as increase in $CD4^+$ counts each year

HR, heart rate.

Table 2. Physiologic Effects of Exercise Interventions in HIV-Infection Populations

Author	Subjects	Number	Intervention	Results
Rigsby et al., 1992	Males, 29–41 yrs old	Total 31: Exercise (n = 16) Counseling (n = 15)	12 weeks for 3 days per week for 1 hour, 20 min cycling at 60–80% max HR followed by 35 minutes of strength and flexibility training	Significant improvements in strength for exercise group only: Chest press (189.4 ± 25.6 vs. 239.7 ± 33.2 n·m) Leg extension (158.7 ± 43.4 vs. 206.3 ± 43.1 n·m) Total time completed during the cycle test (996.15 ± 170.43 vs. 1388.46 ± 224.45 s)
Wagner et al., 1998	Males	Total 29: Resistance (n = 10) Cardiovascular (n = 2)	Exercised an average of 3.4 days per week, for an average of 87 minutes, at an average intensity of 6.1 out of 8	Significant ($p < 0.000$) improvement in lean body mass (61.6 ± 7.2 vs. 64.2 ± 8.2 kg) for exercise group
Roubenoff et al., 1999	Males and females, 25–56 yrs old	Total 25: Males (n = 20) Females (n = 5) With wasting (n = 6) Without wasting (n = 19)	3 sets of 8 repetitions for 8 weeks with week 1 repetitions at 50% RM, week 2 repetitions at 60% RM, and week 3–8 at 75–80% RM	Significant ($p < 0.0002$) increase in lean body mass (1.75 ± 1.94 kg) Significant percent increases in strength (as tested by 1-RM) on the: Chest press (31 ± 18%) Leg press (40 ± 23.6%) Upper back (50 ± 27%) Quadriceps extension (38 ± 31%). Significant ($p < 0.05$) decrease in fat mass (0.92 ± 2.22 kg)
Terry et al., 1999	Males and females, 23–39 yrs old	Total 21: Females (n = 17) High-intensity (n = 11) Moderate-intensity (n = 10)	12 weeks of treadmill training at 60% max HR (moderate) or 84% max HR (high) 3 times per week for 30 minutes	Functional capacity significantly improved in moderate intensity group 680 ± 81 vs. 750 ± 151s and high intensity group 651 ± 122 vs. 841 ± 158s
Bhasin et al., 2000	Males, 18–50 yrs old/w 5% loss of BW	Total 49: Placebo (n = 12) Testosterone (n = 15) Exercise + placebo (n = 11), Exercise + testosterone (n = 11)	3 exercise sessions per week for 16 weeks, weeks 1–4 60% 1-RM for 12–15 repetitions, weeks 5–10, 4 sets of 4–6 repetitions at 90% 1-RM intensity on heavy days, 80% 1-RM on medium days, and 70% 1-RM on light days	Significant increase in strength with exercise only (29–36%) and with testosterone only (17–28%) Significant increase in thigh muscle volume in the testosterone only (40 cm^3, ($p < 0.001$) and the exercise only group (62 cm^3, $p = 0.03$)
Grinspoon et al., 2000	Males with AIDS wasting	Total 43: Placebo (n = 12) Placebo + exercise (n = 10), Testosterone (n = 10) Testosterone + exercise (n = 11)	3 exercise sessions per week for 12 weeks consisting of 20 minutes on stationary bicycle at 60–70% age predicted max HR, week 1 & 2, 2 sets 8 repetitions at 60% RM, weeks 3–6, 2 sets 8 repetitions 70%, weeks 7–12, 3 sets 8 repetitions at 80%	Significant increase in LBM: 2.3 kg with training 4.2 kg with/training + testosterone

Fairfeld et al., 2001	Males with AIDS wasting	Total 43: Placebo (n = 12) Testosterone (n = 10) Placebo + training (n = 10) Testosterone + training (n = 11)	3 times per week for 12 weeks, 30 minutes on stationary bicycle at 60–70% age predicted max HR, week 1 & 2, 2 sets 6–8 repetitions at 60% 1 RM, week 3–6, 2 sets 6–8 repetitions at 70%, week 7–9, 2 sets 6–8 repetitions at 70% and 1 set 80%, week 10–12, 3 sets 6–8 repetitions at 80%	Significant increase in thigh muscle area and attenuation with testosterone and training
Roubenoff and Wilson, 2001	Males and females	Total 25: Females (n = 5) Males w/wasting (n = 6) Males and females w/o wasting (n = 19)	3 times per week for 8 weeks, performed 3 sets of 8 repetitions at 80% 1-RM	Significant increase ($p < 0.0001$) in strength for wasting group (60%) and nonwasting group (44%) Significant, 2.3% increase in LBM in nonwasted group, wasted group had 5.3% improvement Significant ($p < 0.05$ improvement on the physical functioning subscale of the SF-36 in wasted group
Sattler et al., 1999 and Sattler et al., 2002	Males over 18 yrs old	Total 30: Nandrolone (n = 15) Nandrolone + exercise (n = 15)	3 sets of 8 repetitions at 80% 1-RM for 12 weeks at 3 times per week	Significant increase ($p < 0.03$) in LDL particle size in nandrolone with exercise group Significant increase ($p < 0.001$) HDL cholesterol and decrease in fasting triglycerides ($p < 0.01$) in the total population Nandrolone only group had a significant increase in body weight (3.2 ± 2.7 kg) and lean body mass (3.9 ± 2.3 kg) Exercise group had significant increases in body weight (4.0 ± 2.0 kg), LBM (5.2 ± 5.7 kg), and significant decrease in fat mass (1.2 ± 1.3 kg) Significant ($p < 0.001$) increases in total thigh, quadriceps, and hamstring muscle volume

(continued)

Table 2. Physiologic Effects of Exercise Interventions in HIV-Infection Populations (Cont'd)

Author	*Subjects*	*Number*	*Intervention*	*Results*
Smith et al., 2001	Males and females	48 total: Females ($n = 8$) Exercise ($n = 18$) Control ($n = 30$)	Aerobic exercise 3 times a week, for 30 minutes a session for 12 weeks	Exercise group significantly reduced BMI ($p < 0.04$), decreased body weight by an average of 1 kg more than the control group Significant reduction of the triceps skinfold ($p < 0.01$), the peripheral skinfolds ($p < 0.02$), the sum of central skinfolds ($p < 0.02$), and reduction of abdominal girth ($p < 0.02$). Vo_{2max} increased in the exercise group by 1.6 mL/kg more than control group

HR, heart rate; RM, repetition maximum; LBM, lean body mass; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BMI, body mass index.

TABLE 3. PSYCHOLOGICAL EFFECTS OF EXERCISE INTERVENTIONS IN HIV-INFECTION POPULATIONS

Author	*Subjects*	*Number*	*Intervention*	*Results*
LaPerriere et al., 1990	Males	Total 23: Exercise (n = 10) Control (n = 13)	45-minutes of aerobic exercise on a stationary bicycle at 80% age predicted max HR	Exercise group had lower anxiety (12.8 ± 2.0 vs. 12.9 ± 2.5) and significantly lower depression (14.0 ± 3.7 vs. 10.9 ± 1.7) scores on the POMS
Stringer et al., 1998	Males and females, 27–45 yrs old	Total 26: Females (n = 3) Control (n = 8), Moderate exercise (n = 9) Heavy exercise (n = 9)	6 weeks of training on stationary bicycle at an increasing work rate from 15–25 W/min until exhaustion, with time adjusted so each group produced the same work, 3 times per week	Significant ($p < 0.01$) improvement in quality of life, hope, and desire to continue living did in both exercise groups
Wagner et al., 1998	Males	Total 29: Resistance (n = 10) Cardiovascular (n = 2)	Exercised an average of 3.4 days per week, for an average of 87 minutes, at an average intensity of 6.1 of 8	Significant ($p < 0.000$) improvements on HAM-D, BSI-total, BSI-depression, Q-LES-Q
Neidig et al., 2003	Males and females	Total 48: Females (n = 3) Exercise (n = 18) Control (n = 30)	See as Smith et al., 2001	Improvement ($p = 0.03$) in CES-D scores, POMS ($p = 0.01$), and depression/rejection subscale ($p = 0.05$)

POMS, Profile of Mood States; HAM-D, Hamilton Depression Scale; BSI-total, Brief Symptom Inventory-distress, depression, anxiety; BSI-depression, Brief Symptom Inventory depression; Q-LES-Q, Endicott Quality of Life Enjoyment and Satisfaction Questionnaire; CES-D, Centers for Epidemiological Studies—Depression Scale.

High-intensity exercise, which was shown to decrease the effectiveness of the immune system for up to 21-hours in a non-HIV–infected population in one study,[68] was previously avoided and moderate-intensity exercise was prescribed. However, Terry et al.[69] later found that high-intensity exercise in an HIV-infected person may not be detrimental to the immune system based on data that showed no difference in $CD4^+$ and $CD8^+$ cell counts after 12 weeks between groups that exercised at 80% maximum rate and 60% maximum heart rate.

Immunologic, physiologic, and psychological effects of aerobic exercise in HIV-infected samples

For these reasons, aerobic training has been used in many different forms as an intervention for HIV-infected persons. LaPerriere and colleagues[70] used an interval training method on a cycle ergometer to examine changes in lymphocyte cell counts in 16 men who began exercising prior to undergoing HIV screening. Patients worked at 70%–80% maximum heart rate for 3 minutes followed by 2-minute sessions at a lower intensity. Findings showed that 45 minutes of training 3 times per week for 5 weeks significantly increased $CD4^+$ helper cell counts (904 vs. 1020 mm^3) and the $CD8^+$-inducer subset $CD45RA^+CD4^+$ (no quantification given) in those who presented as HIV positive.

LaPerriere and coworkers[71] also exercised HIV-infected males, 18–40 years of age, on cycle ergometers 3 times per week for 45 minutes per session at 70%–80% maximum age-predicted heart rate for 10 weeks. After comparing preexercise to postexercise blood lymphocyte levels, a significant increase was observed in $CD2^+$ (1717 vs. 2183 mm^3), $CD4^+$ (942 vs. 1280 mm^3), $CD8^+$ (655 vs. 816 mm^3), $CD45RA^+CD4^+$ (312 vs. 955 mm^3), and $CD20^+$ (162 vs. 244 mm^3) cell counts. These studies by LaPerriere and associates[71] are unique in that they are the only two to show an actual increase in lymphocyte populations. Other studies have shown that exercise does not decrease lymphocyte numbers,[5,48,52] as well as showing that exercise may attenuate the decrease in lymphocytes that occurs with normal disease progression,[51] but none have shown an increase in cell numbers. This observed increase might actually be the measurement of the mobilization of cells from the lymphoid tissue, rather than an actual increase in cell quantity.

Mustafa and colleagues[72] also addressed $CD4^+$ cell counts while performing a longitudinal study on 415 homosexual males (156 HIV-infected [$CD4^+$ count 555 + 304] and 259 HIV-negative [988 + 380] at the time of enrollment) from 1985–1991 aimed at examining the association between exercise and HIV disease progression. Of the 156 HIV-infected men sampled, 68 progressed to AIDS, and 49 died of AIDS-related complications. Individuals were asked how many times per week they exercised, with an answer of 3–4 times per week being considered the minimum for inclusion in the exercise group and those who exercised less considered nonexercisers. Using a linear combination of parameter estimates, it was found that exercise slowed progression to AIDS and time to death with AIDS. Simple linear regression using $CD4^+$ cell counts as the dependent variable, showed that CD4 counts increased 1 year, and had a lesser decline in other years compared to the nonexercising group.

MacArthur and colleagues[73] evaluated various immunologic and cardiovascular parameters of 25 HIV-infected persons (24 males and 1 female), currently on antiretroviral therapy, following a 24-week exercise program. Subjects who exercised at 50%–60% $V_{O_{2max}}$ in four 10-minute intervals comprised the low-intensity group, and a high-intensity group worked at 75%–85% $V_{O_{2max}}$ for six 4-minute intervals. Both groups performed exercise 3 times per week on a treadmill, stationary bicycle, rower, or stair-stepper. The 6 individuals who completed the program, 3 in each group, showed no significant change in $CD4^+$ cell counts at week 24 (185 vs. 195 cells per microliter), however, significant improvements were seen in $V_{O_{2max}}$ (33.2 + 3.3 vs. 41.2 + 4.9 mL/kg per minute), submaximal heart rate (137 + 8 vs. 124 + 7 beats per minute), and Relative Perceived Effort (RPE) (12.2 + 2.4 vs. 8.5 + 1.4). Individual group data were not analyzed because of small number of subjects who completed the intervention resulted in low power to detect group differences.

Aerobic exercise interventions have also been designed to evaluate changes in body

composition and fatigue indices. Smith et al.[74] implemented a regimen of 30-minute exercise sessions 3 times per week for 12 weeks for 60 HIV-infected individuals (52 males and 8 females). Workloads were set at 60%–80% Vo_{2max} and were increased as needed to keep the subject's heart rates within set parameters. Forty-nine subjects (75% taking antiretrovirals) completed the program and showed a 1-minute increase in time to fatigue on a treadmill (a measure of physical endurance). Subjects in the exercise group significantly reduced body mass index ($p < 0.04$) and decreased body weight by an average of 1 kg more than the control group (1.5 kg lost vs. 0.5 kg lost). Included in the loss of body weight was a significant reduction of the triceps skinfold ($p < 0.01$), the peripheral skinfolds ($p < 0.02$), and the sum of central skinfolds ($p < 0.02$), as well as a reduction of abdominal girth ($p < 0.02$). Vo_{2max} increased in the experimental group by 2.6 mL/kg compared to a 1 mL/kg increase in the control group.

Terry et al.[69] divided aerobically exercising groups into a moderate intensity group who worked at 60% maximal heart rate ($n = 11$) and high intensity group who exercised at 84% maximal heart rate ($n = 10$). Subjects were seen 3 times per week, and each session lasted approximately 1 hour with the first 15 minutes and the last 15 minutes devoted to stretching and the remaining 30 minutes consisting of treadmill exercise at the prescribed intensity. At the completion of the 12-week study, functional capacity, as measured by time to fatigue on a maximal exercise test, increased in both groups but more so in the high intensity group (680 + 81 vs. 750 + 151 seconds for the moderate-intensity group and 651 + 122 vs. 841 + 158 seconds for the high-intensity group), while no changes in body fat were observed. Immunologic variables such as $CD4^+$ cells (592 vs. 614 vs. 683 mm^3), $CD8^+$ cells (1030 vs. 1242 vs. 1252 mm^3), leukocytes (6344 vs. 6400 vs. 6930 mm^3) and lymphocytes (2148 vs. 2627 vs. 2638 mm^3) increased at 6 and 12 weeks, respectively, but were not statistically significant. Depression scores, as obtained with the Montgomery-Asberg scale for depression, remained unchanged from preintervention to postintervention. These results, however, lack authority because of low statistical power to detect changes.

Aerobic exercise has also been linked to improvements in the psychological health of HIV-infected persons. Stringer and others[5] evaluated immune indices and quality-of-life scores before and after a 6-week exercise program. Twenty-six HIV-infected individuals, 24 of whom were on antiretroviral therapy, were divided into a control group ($n = 8$), a moderate-intensity exercise group ($n = 9$), and a high-intensity exercise group ($n = 9$). Aerobic training, consisting of 6 weeks of 3 sessions per week on a stationary bicycle, was prescribed with the moderate-intensity group working approximately 60 minutes per session and the high-intensity group working less time, approximately 30–40 minutes, to produce equal work. Results showed no significant change in $CD4^+$ count (moderate, 297 vs. 310 mm^3, heavy, 342 vs. 339 mm^3) or viral load (moderate, 56,101 vs. 45,698/mL; heavy: 11,706 vs. 10,326/mL) in any group, but quality of life scores in the areas of quality of life, hope, and desire to continue living did significantly ($p < 0.01$) improve in both exercise groups.

LaPerriere and colleagues[75] recruited 50 homosexual males unaware of their HIV status to exercise prior to learning their HIV status. Exercise was performed on a cycle ergometer for 45 minutes, with 3-minute stages at 80% age predicted maximum heart rate alternated with 2-minute stages at 60%–79% predicted maximal heart rate. Based on results from the Profile of Mood States and the State-Trait Anxiety Inventory, the 10 men in the exercise group who were diagnosed HIV positive had lower anxiety (12.8 + 2.0 vs. 12.9 + 2.5) and depression (14.0 + 3.7 vs. 10.9 + 1.7) scores than did those HIV-positive men who did not exercise. Nonexercisers also had a decrease in $CD4^+$ cell number (61 cells/mm^3) that was blunted in the exercise group (increase of 38 cells/mm^3).

The effects of aerobic exercise on depression in HIV-infected individuals were studied by Neidig and colleagues.[76] The 49 subjects who completed the previously mentioned study by Smith et al. were also given tests to determine depression levels using the Center for Epidemiological Studies-Depression Scale (CES-D), the Beck Depression Inventory (BDI), Pro-

file of Mood States (POMS), and stress was assessed with the Perceived Stress Scale 4 (PSS-4). Those who completed the exercise intervention showed significant improvement in CES-D scores ($p = 0.03$), the 65-item POMS ($p = 0.01$), and on the depression/rejection subscale ($p = 0.05$).

Physiologic effects of resistance training in HIV-infected samples

To assess the ability of the HIV-infected person to adapt to load, Roubenoff and coworkers[77] prescribed an 8-week regimen of 3 weekly sessions consisting of resistance training with 3 sets of 8 repetitions performed at 80% of the subjects' 1-RM. The men ($n = 20$) and women ($n = 5$), all of whom were taking antiretroviral therapy, rated the difficulty of each exercise set on the Borg RPE Scale, and resistance was increased the following session if the RPE was less than 16. At the conclusion of the 8-week intervention, there was a significant ($p < 0.0002$) increase in lean body mass (1.75 + 1.94 kg), and strength (as tested by 1-RM) on the chest press (31 + 18%), leg press (40 + 23.6%), upper back (50 + 27%), and quadriceps extension (38 + 31%). There was also a significant ($p < 0.05$) decrease in fat mass (0.92 + 2.22 kg), while overall body weight remained the same.

Roubenoff and Wilson[1] next compared the effects of progressive resistance training (PRT) on physical functioning in wasted ($n = 6$) and nonwasted ($n = 19$) HIV-infected populations. The wasted group was classified by involuntary weight loss of greater than 10% baseline body weight, fewer documented for more than 30 days, chronic weakness, and/or chronic diarrhea independent of any conditions other than HIV-infected that may lead to weight loss.[78] Three subjects with wasting were on antiretroviral therapy and 10 nonwasted subjects were on antiretroviral therapy. The training regimen was consistent with the previous study (3 sessions per week for 8 weeks, with subjects performing 3 sets of 8 repetitions at 80% 1-RM on the chest press, leg press, leg extension, and upper back machines). A significant increase ($p < 0.0001$) in strength, assessed by average 1-RM on four machines, was observed in the wasting group (60% increase) and the nonwasting group (44% increase). A significant, 2.3% increase in lean body mass (LBM) was observed in the nonwasted group, while the wasted group exhibited at 5.3% improvement. Wasted subjects also had a significant ($p < 0.05$) 6-point improvement on the physical functioning subscale of the Medical Outcomes Study (MOS) Short Form 36 (SF-36) questionnaire.

The effects of resistance exercise, along with whey protein supplementation, was tested in 30 HIV-infected women by Agin et al.[79] Subjects were divided into a protein only group ($n = 10$), an exercise only group ($n = 10$), and a combined therapy group ($n = 10$). After a 6-week control period, 14 weeks of resistance training was implemented. Results showed no significant changes in strength or quality of life (QOL) during the control period. Protein only patients gained 3.6 kg ($p = 0.001$), and 2.5 kg of fat ($p = 0.002$), with no change in skeletal muscle mass (0.6 kg; $p = 0.12$). The exercise-only group increased skeletal muscle mass (1.2 kg; $p < 0.001$) and decreased fat mass (1.7 kg; $p = 0.02$). The combined therapy group had no change in skeletal muscle (0.6 kg; $p = 0.30$). Strength increased for both exercise groups (40.6 to 95.3%; $p < 0.001$). The QOL physical activity score improved for the exercise group ($p = 0.02$) and worsened for protein group ($p = 0.01$).

Physiologic effects of combined aerobic and resistance training in HIV-infected samples

The combination of aerobic and resistance training has been used to treat HIV-infected persons. Rigsby and colleagues[80] subjected 16 patients to a 12-week exercise program consisting of 3 visits per week, and 15 patients attended 1.5 to 2 hour counseling sessions at least 1 time per week during the same 12-week period. Subjects in the exercise group performed 20 minutes of aerobic exercise on a stationary bicycle at 60%–80% maximum heart rate followed by 35 minutes of combined strength and flexibility exercises. Strength training was conducted on a hydraulic isokinetic weight-training machine and 3 sets were limited to no more than 30 repetitions total. The results showed that subjects in the exercise group significantly improved muscular strength in the chest press

(189.39 + 25.58 vs. 239.66 + 33.24 n·m newton-meter) and the leg extension (158.74 + 43.43 vs. 206.28 + 43.06 Newton-meter (n·m) while also improving cardiorespiratory fitness, as measured by total time completed during the cycle test (996.15 + 170.43 vs. 1388.46 + 224.45 seconds), but no improvements were seen in the counseling group. Measurement of immune markers showed no significant effect of either counseling or exercise on total leukocytes, total lymphocytes, $CD4^+$, or $CD8^+$ cell counts.

Physiologic effects of exercise and anabolic supplementation

It has become common practice to combine progressive resistance training and anabolic supplementation when treating AIDS patients. These treatments are effective in increasing body weight, but they have been shown to cause liver toxicity and elevated serum lipid levels, thus strict monitoring is required.[81] Grinspoon and colleagues[82] showed that greater increases in LBM occurred when combining testosterone and exercise as compared to testosterone treatment alone. Subjects with AIDS wasting were divided into four study groups: placebo with no exercise ($n = 12$), placebo with exercise ($n = 10$), testosterone with no exercise ($n = 10$), testosterone with exercise ($n = 11$). Participants placed in the testosterone groups received intramuscular testosterone enanthate injections (200 mg/wk) for the 12-week duration of the study. The exercise groups trained 3 times per week, beginning each session with 20 minutes of aerobic exercise followed by resistance training. Resistance training involved 6 exercises (3 lower body and 3 upper body). Training was conducted as follows: weeks 1 and 2, 2 sets of 8 repetitions at 60% 1-RM; weeks 3 through 6, 2 sets of 8 repetitions at 70% 1-RM; weeks 7 through 12, 3 sets of 8 repetitions at 80% 1-RM. LBM significantly increased with training, independent of testosterone (2.3 kg), and with testosterone an increase of 4.2 kg increase was observed. Isometric strength testing showed no effect of training or testosterone, but trained subjects did double their training volume.

Bhasin and others[83] showed that testosterone and exercise independently increased LBM and muscular strength in 16 weeks, although no additive effect was observed. Forty-nine HIV-infected males, 18–50 years of age with low serum testosterone levels and a 5% or greater weight loss in the previous 6 months completed the study. Subjects in the exercise groups trained 3 times per week at 60% of their 1-RM for 3 sets of 12–15 repetitions for the first 4 weeks. Weeks 5–10 consisted of 4 sets of 4–6 repetitions, with a 90% 1-RM intensity on heavy days, 80% 1-RM on medium days, and 70% 1-RM on light days. A similar pattern was followed for the remaining weeks, with upper body exercise resistance being increased by 7% and lower body resistance by 12%. Subjects in the exercise alone group showed a 29%–36% increase in strength, while the testosterone only group showed a 17%–28% increase, but there was no additive effect of the two therapies combined. Thigh muscle volume increased by 40 cm^3 ($p < 0.001$) in the testosterone-only group, by 62 cm^3 ($p < 0.003$) in the exercise-only group, and volume increased by 44 cm^3 ($p < 0.001$) in the combined therapy group. Body weight significantly increased in the testosterone only group ($p < 0.001$), but did not change in the other two groups receiving therapy. There was no additive effect of the two therapies on LBM, however, both the testosterone-only ($p < 0.05$) and exercise-only ($p < 0.04$) increased significantly.

Sattler and others[84] had 14 subjects perform 3 sets of 8 repetitions of resistance exercise at 80% 1-RM, while simultaneously treating them with a 200-mg injection of nandrolone decanoate (anabolic steroid) during week 1, 400 mg for week 2, and 600 mg for the remainder of the exercise intervention; 14 other subjects received only the nandrolone deconoate. After 12 weeks, the nandrolone-only group had a significant increase in body weight (3.2 + 2.7 kg) and lean body mass (3.9 + 2.3 kg), but no significant change in body fat. The exercise group also had significant increases in body weight (4.0 + 2.0 kg) and lean body mass (5.2 + 5.7 kg), which were greater than those observed in the steroid only group, as well as a significant decrease in fat mass (1.2 + 1.3 kg). Both groups also showed significant ($p < 0.001$) increases in total thigh, quadriceps, and hamstring muscle area.

Wagner et al.[85] recruited 54 men to partici-

pate in biweekly treatments of testosterone at 200 mg during weeks 1 and 2, and 400 mg during weeks 3–8. Prior to the intervention, and again at week 12, psychiatrists administered the Structural Clinical Inventory (used to diagnose mood disorders), the Hamilton Rating Scale for Depression (HAM-D), the Brief Symptom Inventory (measures distress [BSI-total], anxiety [BSI-anxiety], and depression [BSI-depression]), and the Endicott Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). Additionally, total body weight, lean body mass, and body fat were measured by bioelectrical impedance at week 0 and week 12. Twenty-nine men reported engaging in exercise during the study, with 10 reporting only resistance exercise and 2 reporting only cardiovascular exercise. These men reported exercising an average of 3.4 days per week, for an average of 87 minutes, at an average intensity of 6.1 of 8, with 8 being the most intense. Exercisers showed significant ($p < 0.000$) improvements in each of the psychological evaluations, while nonexercisers showed a significant ($p < 0.000$) improvement in only the HAM-D. The nonexercisers exhibited no changes in body composition, while the exercisers had a significant ($p < 0.000$) improvement in lean body mass (61.6 + 7.2 vs. 64.2 + 8.2 kg).

In addition to skeletal muscle adaptations and changes in fat mass, exercise and testosterone used in combination can cause other metabolic changes. Using the exercise and nandrolone deconoate treatment schedule as previously discussed,[75] Sattler et al.[86] evaluated the effects of nandrolone on various risk factors of cardiovascular disease. Measurement at week 12 showed a significant increase ($p < 0.03$) in low-density lipoprotein (LDL) particle size in the nandrolone and exercise group, as well as in total high-density lipoprotein (HDL) cholesterol in the total population ($p < 0.001$). The LDL changes returned to no significance at week 24, while the total HDL remained significantly higher ($p < 0.01$) in the exercise-group only. Fasting triglycerides were significantly reduced ($p < 0.01$) in the total population at week 12, but this was not sustained throughout the 24-week study. These results do not allow for a definitive statement as to the efficacy of anabolic therapy in HIV-infected persons in terms of cardiovascular disease risk factors.

Forty-three HIV-infected men with AIDS wasting syndrome were recruited by Fairfield et al.[87] to participate in this study. The men were randomly assigned to the following groups: placebo with no training ($n = 12$), testosterone (200 mg/wk) with no training ($n = 10$), placebo with training ($n = 10$), and testosterone (200 mg/wk) with training ($n = 11$). The exercise protocol consisted of 3 sessions per week for 12 weeks. Each workout consisted of 30 minutes on a stationary bicycle at 60%–70% the subjects age predicted maximum heart rate. The resistance exercise for weeks 1 and 2 included 2 sets of 6–8 repetitions at 60% 1-RM; weeks 3 to 6, 2 sets of 6–8 repetitions at 70%; weeks 7 to 9, 2 sets of 6–8 repetitions at 70% and 1 sets 80%; and weeks 10 to 12, 3 sets of 6–8 repetitions at 80%. Both testosterone therapy and exercise were found to increase thigh muscle attenuation, while the combination proved to elicit the greatest increase (no data).

No research that examines the effects of lower intensity resistance exercise in HIV-infected populations has been found. The physiologic benefits of resistance training can be attained at intensities below 80% 1-RM, yet investigators have failed to examine this type of training. The rationale for using 80% 1-RM for a resistance training protocol is not described by the researchers, but may stem from recommendations by agencies such as the ACSM, which state that resistance exercise above 80% 1-RM is beneficial for rapid gains in strength.[37] The ACSM manual goes on to say that resistance exercise at 40%–60% 1-RM is sufficient for the development of strength, again begging the question as to why this intensity of training has not been tested.[37]

DISCUSSION

More attention is needed to determine the type, duration, frequency, and intensity of exercise needed to elicit physiologic and psychological changes in the HIV-infected population. It is evident that no distinct connection has been made between exercise duration and intensity on $CD4^+$ cell counts,[5,48–52] leaving more research to be done regarding exercise and immune indices in the HIV-infected person. These cell counts can differ by compartment and time

after exercise, so researchers need to be consistent in retrieving data so true comparisons can be made. Furthermore, mixed results have been obtained regarding aerobic exercise prescription and psychological evaluations.[5,54,55] Studies of this nature should include a control group that attends some form of therapy for the same amount of time the exercise group is in contact with the research team. Additionally, with prevalence rates as high as 28%,[19] some consideration should be given to examining the effects of exercise in the HIV-infected anemic.

Inflammatory and repair mechanisms of the trained muscle of HIV-infected persons have yet to be fully documented. Changes in inflammatory cytokines (IL-1, IL-6, TNF-α) with HIV-infection, as well as the presence of chronic inflammatory markers caused by chronic infection, may alter the healing process, and consequently, the adaptive ability of muscle to stress. Muscle biopsy would provide invaluable insight into these, and many other questions surrounding muscle in an HIV-infected host.

Finally, a major problem with a number of these studies is low statistical power and major threats to internal validity. The problems can be attributed to differential attrition, with nonequivalent treatment and control groups. Validity of the control groups is also compromised by not having the same amount of personal interaction between treatment and control groups. Error is also present when using heart rate as a measure of work rate because cardiac neuropathy is common to many HIV-infected persons. All study designs should include a nutritional assessment to rule diet out as a confounding variable. Improvement in study design would allow for better comparisons between studies, and may help to explain discrepancies that exist among them, particularly in terms of impact on $CD4^+$ cells.

Study sample characteristics also limit the generalizability of many of these studies. Many studies have been done only using males, leaving the effects of exercise on females relatively unknown.

CONCLUSION

Current research shows that high- and moderate-intensity aerobic training and resistance training implemented by trained professionals are both safe and effective in HIV-infected persons. The intervention studies reviewed in this paper have shown the ability to increase muscular strength and endurance, improve body composition, and improve mood while not adversely compromising the immune system. For persons suffering from symptoms, exhaustive exercise should be avoided, but activity of moderate intensity is still encouraged. It should be noted that all HIV-infected individuals and their trainers should be in constant contact with the patient's physician regarding progress and changes in health and performance levels. Programs should be designed in accordance with the ACSM guidelines for exercise testing and prescription, and careful attention should be given to avoid overtraining.

REFERENCES

1. Roubenoff R, Wilson IB. Effect of resistance training on self-reported physical functioning in HIV infection. Med Sci Sports Exerc 2001;33:1811–1817.
2. Spence DW, Galantino ML, Mossberg KA, Zimmerman SO. Progressive resistance exercise: Effect on muscle function and anthropometry of a select AIDS population. Arch Phys Med Rehabil 1990;71:644-648.
3. Yarasheski KE, Roubenoff R. Exercise treatment for HIV-associated metabolic and anthropomorphic complications. Exerc Sport Sci Rev 2001;29:170–174.
4. Birk TJ, McGrady A, MacArthur RD, Khuder S. The effects of massage therapy alone and in combination with other complementary therapies on immune system measures and quality of life in human immunodeficiency virus. J Altern Complement Med 2000;6: 405–414.
5. Stringer WW, Berezovskaya M, O'Brien WA, Beck CK, Casaburi R. The effect of exercise training on aerobic fitness, immune indices, and quality of life in HIV+ patients. Med Sci Sports Exerc 1998;30:11–16.
6. Wheeler DA, Gibert CL, Launer CA, et al. Weight loss as a predictor of survival and disease progression in HIV infection. Terry Beirn Community Programs for Clinical Research on AIDS. J Acquir Immune Defic Syndr Hum Retrovirol 1998;18:80–85.
7. Carr A, Samaras K, Chrisholm DJ, Cooper DA. Abnormal fat distribution and use of protease inhibitors. Lancet 1998;351:1736.
8. Scevola D, Di Matteo A, Uberti F, Minoia G, Poletti F, Faga A. Reversal of cachexia in patients treated with potent antiretroviral therapy. AIDS Read 2000; 10:365.
9. Ranganathan S, Kern PA. The HIV protease inhibitor saquinavir impairs lipid metabolism and glucose transport in cultured adipocytes. J Endocrinol 2002; 172:155–162.

10. Roubenoff R, Schmitz H, Bairos L, et al. Reduction of abdominal obesity in lipodystrophy associated with human immunodeficiency virus infection by means of diet and exercise: case report and proof of principle. Clin Infect Dis 2002;34:390–393.
11. Breitkreutz R, Wagner J, Tokus M, et al. Flux of amino acids and energy substrates across the leg in weight-stable HIV-infected patients with acute opportunistic infections: Indication of a slow protein wasting process. J Mol Med 2001;79:671–678.
12. Grunfeld C, Pang M, Shimizu L, Shigenaga JK, Jensen P, Feingold KR. Resting energy expenditure, caloric intake, and short-term weight change in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. Am J Clin Nutr 1992;55: 455–460.
13. Macallan DC, Noble C, Baldwin C, et al. Energy expenditure and wasting in human immunodeficiency virus infection. N Engl J Med 1995;333:83–88.
14. Melchior JC. Metabolic aspects of HIV: Associated wasting. Biomed Pharmacother 1997;51:455–460.
15. Semba RD, Shah N, Klein RS, Mayer KH, Schuman P, Vlahov D. Prevalence and cumulative incidence of and risk factors for anemia in a multicenter cohort study of human immunodeficiency virus-infected and -uninfected women. Clin Infect Dis 2002;34:260–266.
16. Camacho J, Poveda F, Zamorano AF, Valencia ME, Vazquez JJ, Arnalich F. Serum erythropoietin levels in anaemic patients with advanced human immunodeficiency virus infection. Br J Haematol 1992;82: 608–614.
17. Northfelt DW. Hematologic aspects of HIV-infection. In: Cohen PT, Sanae MA, Volberding PA, eds. The AIDS Knowledge Base: A Textbook on HIV Diseases from the University of California, San Francisco and the San Francisco General Hospital. Philadelphia: Williams & Wilkins, 1999:505–514.
18. Orlando M, Burnam MA, Beckman R, et al. Re-estimating the prevalence of psychiatric disorders in a nationally representative sample of persons receiving care for HIV: Results from the HIV Cost and Services Utilization Study. Int J Methods Psychiatr Res 2002; 11:75–82.
19. Heckman TG, Heckman BD, Kochman A, Sikkema KJ, Suhr J, Goodkin K. Psychological symptoms among persons 50 years of age and older living with HIV disease. Aging Ment Health 2002;6:121–128.
20. Penzak SR, Reddy YS, Grimsley SR. Depression in patients with HIV infection. Am J Health Syst Pharm 2000;57:376–386.
21. Evans DL, Ten Have TR, Douglas SD, et al. Association of depression with viral load, CD8 T lymphocytes, and natural killer cells in women with HIV infection. Am J Psychiatry 2002;159:1752–1759.
22. Maes M, Van Bockstaele DR, Gastel A, et al. The effects of psychological stress on leukocyte subset distribution in humans: Evidence of immune activation. Neuropsychobiology 1999;39:1–9.
23. Leonard B. Stress, depression and the activation of the immune system. World J Biol Psychiatry 2000;1:17–25.
24. Leserman J, Petitto JM, Gu H, et al. Progression to AIDS, a clinical AIDS condition and mortality: Psychosocial and physiological predictors. Psychol Med 2002;32:1059–1073.
25. Turner BJ, Laine C, Cosler L, Hauck WW. Relationship of gender, depression, and health care delivery with antiretroviral adherence in HIV-infected drug users. J Gen Intern Med 2003;18:248–257.
26. Tucker JS, Burnam MA, Sherbourne CD, Kung FY, Gifford AL. Substance use and mental health correlates of nonadherence to antiretroviral medications in a sample of patients with human immunodeficiency virus infection. Am J Med 2003;114:573–580.
27. Angelino AF, Treisman GJ. Management of psychiatric disorders in patients infected with human immunodeficiency virus. Clin Infect Dis 2001;33:847–856.
28. Singh N, Squier C, Sivek C, Wagener M, Nguyen MH, Yu VL. Determinants of compliance with antiretroviral therapy in patients with human immunodeficiency virus: Prospective assessment with implications for enhancing compliance. AIDS Care 1996;8: 261–269.
29. Rabkin JG, Johnson J, Lin SH, et al. Psychopathology in male and female HIV-positive and negative injecting drug users: longitudinal course over 3 years. AIDS 1997;11:507–515.
30. Hogg RS, Heath KV, Yip B, et al. Improved survival among HIV-infected individuals following initiation of antiretroviral therapy. JAMA 1998;279:450–454.
31. Vanhove GF, Schapiro JM, Winters MA, Merigan TC, Blaschke TF. Patient compliance and drug failure in protease inhibitor monotherapy. JAMA 1996;276: 1955–1956.
32. Descamps D, Flandre P, Calvez V, et al. Mechanisms of virologic failure in previously untreated HIV-infected patients from a trial of induction-maintenance therapy. Trilege (Agence Nationale de Recherches sur le SIDA 072 Study Team). JAMA 2000;283:205–211.
33. Little SJ, Daar ES, D'Aquila RT, et al. Reduced antiretroviral drug susceptibility among patients with primary HIV infection. JAMA 1999;282:1142–1149.
34. Boden D, Hurley A, Zhang L, et al. HIV-1 drug resistance in newly infected individuals. JAMA 1999; 282:1135–1141.
35. Brooks GA, Fahey TD, White TP. Human Bioenergetics and its Applications, 2nd ed. Mountain View, CA: Mayfield Publishing Company, 1996.
36. Maughan R, Gleeson M, Greenhaff P. Biochemistry of Exercise and Training. New York: Oxford University Press, Inc., 1997.
37. ACSM's Guidelines for Physical Fitness, Testing, and Interpretation, 6th ed. Philadelphia: Lippincott, Williams & Wilkins, 2000.
38. Villa A, Foresti V, Confalonieri F. Autonomic neuropathy and prolongation of QT interval in human immunodeficiency virus infection. Clin Auton Res 1995;5:48–52.
39. Schneider SH, Elouzi EB. The role of exercise in type II diabetes mellitus. Prev Cardiol 2000;3:77–82.
40. Gordon NF, Scott CB, Wilkinson WJ, Duncan JJ, Blair

SN. Exercise and mild essential hypertension. Recommendations for adults. Sports Med 1990;10:390–404.
41. Berlin JA, Colditz GA. A meta-analysis of physical activity in the prevention of coronary heart disease. Am J Epidemiol 1990;132:612–628.
42. Adamsen L, Midtgaard J, Rorth M, et al. Feasibility, physical capacity, and health benefits of a multidimensional exercise program for cancer patients undergoing chemotherapy. Support Care Cancer 2003; 11:707–716.
43. Stenstrom CH, Minor MA. Evidence for the benefit of aerobic and strengthening exercise in rheumatoid arthritis. Arthritis Rheum 2003;49:428–434.
44. LaStayo PC, Ewy GA, Pierotti DD, Johns RK, Lindstedt S. The positive effects of negative work: Increased muscle strength and decreased fall risk in a frail elderly population. J Gerontol A Biol Sci Med Sci 2003;58:M419–M424.
45. Siu PM, Donley DA, Bryner RW, Always SE. Citrate synthase expression and enzyme activity after endurance training in cardiac and skeletal muscles. J Appl Physiol 2003;94:555–560.
46. Schulte JN, Yarasheski KE. Effects of resistance training on the rate of muscle protein synthesis in frail elderly people. Int J Sport Nutr Exerc Metab 2001;11 (suppl):S111–S118.
47. Gabriel H, Schwarz L, Born P, Kindermann W. Differential mobilization of leucocyte and lymphocyte subpopulations into the circulation during endurance exercise. Eur J Appl Physiol Occup Physiol 1992;65: 529–534.
48. Moyna NM, Acker GR, Weber KM, et al. The effects of incremental submaximal exercise on circulating leukocytes in physically active and sedentary males and females. Eur J Appl Physiol Occup Physiol 1996; 74:211–218.
49. Nieman DC, Nehlsen-Cannarella SL, Donohue KM, et al. The effects of acute moderate exercise on leukocyte and lymphocyte subpopulations. Med Sci Sports Exerc 1991;23:578–585.
50. Fry RW, Morton AR, Crawford GP, Keast D. Cell numbers and in vitro responses of leucocytes and lymphocyte subpopulations following maximal exercise and interval training sessions of different intensities. Eur J Appl Physiol Occup Physiol 1992;64:218–227.
51. McCarthy DA, Dale MM. The leucocytosis of exercise. A review and model. Sports Med 1988;6:333–363.
52. Miles MP, Leach SK, Kraemer WJ, Dohi K, Bush JA, Mastro AM. Leukocyte adhesion molecule expression during intense resistance exercise. J Appl Physiol 1998;84:1604–1609.
53. Nieman DC, Ahle JC, Henson DA, et al. Indomethacin does not alter natural killer cell response to 2.5 h of running. J Appl Physiol 1995;79:748–755.
54. Hinton JR, Rowbottom DG, Keast D, Morton AR. Acute intensive interval training and in vitro t-lymphocyte function. Int J Sports Med 1997;18:130–135.
55. Frisina JP, Gaudieri S, Cable T, Keast D, Palmer TN. Effects of acute exercise on lymphocyte subsets and metabolic activity. Int J Sports Med 1994;15:36–41.
56. Shinkai S, Shore S, Shek PN, Shephard RJ. Acute exercise and immune function. Relationship between lymphocyte activity and changes in subset counts. Int J Sports Med 1992;13:452–461.
57. Rhind SG, Shek PN, Shinkai S, Shephard RJ. Effects of moderate endurance exercise and training on in vitro lymphocyte proliferation, interleukin-2 (IL-2) production, and IL-2 receptor expression. Eur J Appl Physiol Occup Physiol 1996;74:348–360.
58. Pedersen BK, Tvede N, Hansen FR, et al. Modulation of natural killer cell activity in peripheral blood by physical exercise. Scand J Immunol 1988;27:673–678.
59. Pedersen BK, Tvede N, Klarlund K, et al. Indomethacin in vitro and in vivo abolishes post-exercise suppression of natural killer cell activity in peripheral blood. Int J Sports Med 1990;11:127–131.
60. Tvede N, Kappel M, Klarlund K, et al. Evidence that the effect of bicycle exercise on blood mononuclear cell proliferative responses and subsets is mediated by epinephrine. Int J Sports Med 1994;15:100–104.
61. Dunn AL, Trivedi MH, O'Neal HA. Physical activity dose-response effects on outcomes of depression and anxiety. Med Sci Sports Exerc 2001;333(6Suppl):S587–S597.
62. Dimeo F, Bauer M, Varahram I, Proest G, Halter U. Benefits from aerobic exercise in patients with major depression: a pilot study. Br J Sports Med 2001;35: 114–117.
63. Lane AM, Lovejoy DJ. The effects of exercise on mood changes: The moderating effect of depressed mood. J Sports Med Phys Fitness 2001;41:539–545.
64. Hale BS, Raglin JS. State anxiety responses to acute resistance training and step aerobic exercise across eight weeks of training. J Sports Med Phys Fitness 2002;42:108–112.
65. Calabrese LH, LaPerriere A. Human immunodeficiency virus infection, exercise and athletics. Sports Med 1993;15:6–13.
66. Roubenoff R. Acquired immunodeficiency syndrome wasting, functional performance, and quality of life. Am J Manag Care 2000;6:1003–1016.
67. Keyser RE, Peralta L, Cade WT, Miller S, Anixt J. Functional aerobic impairment in adolescents seropositive for HIV: A quasiexperimental analysis. Arch Phys Med Rehabil 2000;81:1479–1484.
68. Nieman DC, Berk LS, Simpson-Westerberg M, et al. Effects of long-endurance running on immune system parameters and lymphocyte function in experienced marathoners. Int J Sports Med 1989;10:317–323.
69. Terry L, Sprinz E, Ribeiro JP. Moderate and high intensity exercise training in HIV-1 seropositive individuals: A randomized trial. Int J Sports Med 1999;20: 142–146.
70. LaPerriere A, Fletcher MA, Antoni MH, Klimas NG, Ironson G, Schneiderman N. Aerobic exercise training in an AIDS risk group. Int J Sports Med 1991;12 (Suppl 1):S53–S57.
71. LaPerriere A, Antoni MH, Ironson G, et al. Effects of aerobic exercise training on lymphocyte subpopulations. Int J Sports Med 1994;(15 Suppl 3):S127–S130.
72. Mustafa T, Sy FS, Macera Ca, et al. Association be-

tween exercise and HIV disease progression in a cohort of homosexual men. Ann Epidemiol 1999;9:127–131.
73. MacArthur RD, Levine SD, Birk TJ. Supervised exercise training improves cardiopulmonary fitness in HIV-infected persons. Med Sci Sports Exerc 1993;25: 684–688.
74. Smith BA, Neidig JL, Nickel JT, Mitchell GL, Para MF, Fass RJ. Aerobic exercise: Effects on parameters related to fatigue, dyspnea, weight and body composition in HIV-infected adults. AIDS 2001;15:693–701.
75. LaPerriere AR, Antoni MH, Schneiderman N, et al. Exercise intervention attenuates emotional distress and natural killer cell decrements following notification of positive serologic status for HIV-1. Biofeedback Self Regul 1990;15:229–242.
76. Neidig JL, Smith BA, Brashers DE. Aerobic exercise training for depressive symptom management in adults living with HIV infection. J Assoc Nurses AIDS Care 2003;14:30–40.
77. Roubenoff R, Weiss L, McDermott A, et al. A pilot study of exercise training to reduce trunk fat in adults with HIV-associated fat redistribution. AIDS 1999;13: 1373–1375.
78. Slutsker L, Castro KG, Ward JW, Dooley SW Jr. Epidemiology of extrapulmonary tuberculosis among persons with AIDS in the United States. Clin Infect Dis 1993;16:513–518.
79. Agin D, Gallagher D, Wang J, Heymsfield SB, Pierson RN, Jr, Kotler DP. Effects of whey protein and resistance exercise on body cell mass, muscle strength, and quality of life in women with HIV. AIDS 2001;15: 2431–2440.
80. Rigsby LW, Dishman RK, Jackson AW, Maclean GS, Raven PB. Effects of exercise training on men seropositive for the human immunodeficiency virus-1. Med Sci Sports Exerc 1992;24:6–12.
81. Schambelan M, Mulligan K, Grunfeld C, et al. Recombinant human growth hormone in patients with HIV-associated wasting. A randomized, placebo-controlled trial. Serostim Study Group. Ann Intern Med 1996;125:873–882.
82. Grinspoon S, Corcoran C, Parlman K, et al. Effects of testosterone and progressive resistance training in eugonadal men with AIDS wasting. A randomized, controlled trial. Ann Intern Med 2000;133:348–355.
83. Bhasin S, Storer TW, Javanbakht M, et al. Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. JAMA 2000;283:763–770.
84. Sattler FR, Schroeder ET, Dube MP, et al. Metabolic effects of nandrolone decanoate and resistance training in men with HIV. Am J Physiol Endocrinol Metab 2002;283:E1214–E1222.
85. Wagner G, Rabkin J, Rabkin R. Exercise as a mediator of psychological and nutritional effects of testosterone therapy in HIV+ men. Med Sci Sports Exerc 1998;30:811–817.
86. Sattler FR, Jaque SV, Schroeder ET, et al. Effects of pharmacological doses of nandrolone decanoate and progressive resistance training in immunodeficient patients infected with human immunodeficiency virus. J Clin Endocrinol Metab 1999;84:1268–1276.
87. Fairfield WP, Treat M, Rosenthal DI, et al. Effects of testosterone and exercise on muscle leanness in eugonadal men with AIDS wasting. J Appl Physiol 2001;90:2166–2171.

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