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Effects of High-Intensity Endurance and Resistance Exercise on HIV Metabolic Abnormalities: A Pilot Study

F. Patrick Robinson, PhD, RN, ACRN
Lauretta T. Quinn, PhD, RN
James H. Rimmer, PhD

The purposes of this pilot study were to examine the effects of a 16-week supervised high-intensity combined endurance and resistance exercise training program on HIV-associated metabolic abnormalities (abdominal adiposity, dyslipidemia, and insulin resistance) and to explore methodological issues related to the design and implementation of the research protocol in preparation for a randomized controlled trial. A one-group pretest-posttest design was used, with outcomes measured at baseline and within 1 week after the conclusion of the training program. The exercise program consisted of 16 weeks (preceded by a 2-week phase-in period) of three endurance sessions (20 min at 70%-80% of VO$_{2\text{max}}$) and two resistance sessions per week (one set of 8-10 repetitions at 80% of one-repetition maximum on seven exercises). Outcome measures included lipid levels (total, high-density lipoprotein, and low-density lipoprotein cholesterol and triglycerides), visceral and subcutaneous adipose area measured by electron beam tomography, fat and lean mass of trunk and limbs measured by dual-energy X-ray absorptiometry, and insulin sensitivity measured by the homeostatic model assessment. Nine participants were recruited, 5 of whom completed the intervention and had pretest and posttest data available for analyses. Aerobic capacity and strength improved over the course of the intervention. Statistically significant decreases were found for total and trunk fat mass (1,324.9 g [±733.6] and 992.8 g [±733.6], respectively). Triglycerides decreased by 59 mg/dL (±69.88), and insulin sensitivity decreased by 15.7% (±41.7%), neither of which was a statistically significant change. Results suggest that further testing of the combined exercise intervention in a randomized controlled design is warranted.

Key words: HIV, exercise, lipids, metabolism, lipodystrophy, adiposity, insulin resistance

Highly active antiretroviral therapy (HAART), while producing dramatic and sustained suppression of viral replication, improved immune function, and reduced morbidity and mortality (Palella et al., 1998, 2004), has also been associated with metabolic changes (increased abdominal adiposity, dyslipidemia, and insulin resistance) that may increase risk for cardiovascular disease (CVD; Grinspoon, 2005; Grinspoon

F. Patrick Robinson, PhD, RN, ACRN, is an assistant professor at the University of Illinois at Chicago, College of Nursing, Department of Medical-Surgical Nursing. Lauretta T. Quinn, PhD, RN, is an associate professor at the University of Illinois at Chicago, College of Nursing, Department of Medical-Surgical Nursing. James H. Rimmer, PhD, is a professor at the University of Illinois at Chicago College of Applied Health Sciences, Department of Disability and Human Development. Address for correspondence: F. Patrick Robinson, PhD, RN, ACRN, University of Illinois at Chicago College of Nursing, Department of Medical-Surgical Nursing (M/C 802), 845 South Damen Avenue, Room 758, Chicago, IL 60612; e-mail: prphd@uic.edu.

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The link between HAART and metabolic abnormalities is unclear and may be a direct result of drug toxicity, immune reconstitution, or longer term survival. Furthermore, HIV itself likely contributes to the etiology of metabolic abnormalities (El-Sadr et al., 2005). Although a matter of concern, existing data do not suggest that the risks of antiretroviral therapy outweigh the benefits. Much to the contrary, disability and death are the highly probable outcomes of untreated HIV infection, whereas the risk of CVD remains small (Bozzette, Ake, Tam, Chang, & Louis, 2003). However, the pathogenesis of CVD occurs over decades, and the current HIV-infected population has been exposed to HAART for a relatively short duration. Longer survival coupled with a high prevalence of traditional CVD risk factors in this same population (age, gender, smoking; Hadigan et al., 2001; Riddler et al., 2003) will likely increase the incidence of CVD associated with HIV disease.

Pharmacological interventions, including the use of certain statins, fibrates, metformin, and thiazolidinediones, are commonly used to manage dyslipidemia and glucose intolerance within the context of HIV disease (Hadigan et al., 2000; Visnegarwala et al., 2004). Although data suggest that these pharmacological agents are safe and modestly effective, they are not without side effects and potential toxicities. Moreover, some patients on HAART must follow complex drug regimens; adding more medications increases patient burden and the likelihood of nonadherence.

Investigation into lifestyle/behavioral changes that may ameliorate metabolic abnormalities in HIV is therefore needed to reduce CVD risk while avoiding the use of CVD medications. Participation in regular moderate- to high-intensity exercise may prove to be an effective first-line treatment strategy for HIV metabolic abnormalities. Clinical and epidemiological research suggests that increased physical activity is associated with improved lipid levels, glucose tolerance, and insulin sensitivity, along with decreased adiposity (Buemann & Tremblay, 1996; Durstine et al., 2001; Ivy, 1997; Ross, Freeman, & Janssen, 2000).

Various groups have investigated exercise as a first-line treatment for HIV-related metabolic abnormalities. Endurance or resistance training alone has produced decreases in triglycerides (Thoni et al., 2002; Yarasheski et al., 2001) and reductions in indices of adiposity (Roubenoff, McDermott, et al., 1999; Smith et al., 2001; Thoni et al., 2002). Likewise, in small, uncontrolled studies, combined endurance and resistance training has been shown to reduce triglyceride levels and trunk adiposity (Jones, Doran, Leatt, Maher, & Pirmohamed, 2001; Roubenoff, Weiss, et al., 1999). The purposes of this pilot study for a randomized controlled trial were to determine the effects of high-intensity endurance and resistance training on HIV-associated fat redistribution, dyslipidemia, and insulin resistance and to explore methodological issues related to the design and implementation of the protocol.

Methods

Design

A one-group pretest-posttest design was used with outcome variables measured at baseline and at the conclusion of a 16-week combined endurance and resistance exercise intervention. Outcome variables were measured the week prior to the start of the phase-in period and during the week following the last exercise session.

Sample

A convenience sample that met the following criteria was recruited: (a) HIV seropositive, (b) treatment with a HAART regimen for at least 24 months, (c) CD4+ lymphocyte number ≥100 cells/mm³, (d) viral load ≤150,000 copies/mm³, (e) aged 30 to 55 years, (f) sedentary (i.e., exercising ≤1 time per week for ≤15 min), (g) evidence of abdominal adipose tissue accumulation using the HIV Outpatient Study cohort assessment (Lichtenstein et al., 2001), and (h) willing and able to exercise 3 days a week. Exclusion criteria included (a) use of lipid-lowering, insulin-sensitizing, or hypoglycemic drugs, anabolic steroids, growth hormone, or megestrol acetate (must be off drug for at least 4 weeks before study entry); (b) current opportunistic infection; (c) diagnosis of diabetes mellitus or coronary artery disease; and (d) orthopedic, muscular, or joint problem that would prevent exercise.

Exercise Intervention

Individuals participated in a 16-week structured endurance and resistance exercise program consisting of 3 supervised sessions per week (48 sessions). All training sessions took place at a research fitness center...
under the supervision of a certified exercise specialist. A schema of the intervention is presented in Table 1.

Each week contained three endurance training sessions consisting of 5-min warm-up and cool-down periods and a 20-min brisk walk, jog, or run on a treadmill to maintain effort at 70% to 80% of maximal oxygen uptake ($VO_{2\text{max}}$). $VO_{2\text{max}}$ was measured via open-circuit spirometry during a maximal exercise test on a treadmill according to American College of Sports Medicine Guidelines (Franklin, 2000) using a modified Bruce protocol (Franklin, 2000). The 70% to 80% $VO_{2\text{max}}$ corresponded to a target heart rate (HR) range (determined by the observed HR at $VO_{2\text{max}}$ during the maximal exercise test). This prescribed intensity is labeled high (American College of Sports Medicine & Roitman, 2001). HR was monitored during each session with a heart rate monitor (chest-band transmitter and wristwatch display).

Two of the three endurance sessions were followed immediately by dynamic resistance training sessions consisting of one set of 8 to 10 repetitions for seven exercises (four upper body and three lower body) performed on stacked-weight machines at an intensity of 80% of one maximal repetition (1-RM; the maximal weight that can be lifted in proper form one time for a specific exercise). Descriptions of each resistance exercise and the affected muscle groups are contained in Table 2. The 1-RM testing was conducted by a certified exercise specialist and retested at the midpoint of the intervention (Week 8), and weight was adjusted to maintain the resistance at 80%.

Preceding the actual 16-week intervention was a 2-week graded phase-in period during which participants increased the intensity and duration of exercises to reach the desired prescription by the end of the 2nd week. The purpose of the phase-in period was to allow participants to acclimate gradually to the exercise prescription. The phase-in period followed the same schedule as the intervention.

A high-intensity endurance prescription was chosen because it has been shown to positively effect dyslipidemia (Durstine et al., 2001) in non-HIV-infected samples. It is not known whether the same is true in HIV, so this prescription seemed logical for pilot work. In regard to the resistance prescription, cumulative evidence suggests that there is little difference in strength gain or muscle hypertrophy between training with one versus multiple sets of repetitions (Carpinelli & Otto, 1998). One set has the added benefit of time efficiency. Published exercise studies that investigated
HIV-related metabolic abnormalities reported positive effects around 12 weeks. Therefore, a 16-week time frame was chosen to determine additional gains.

**Outcome Variables**

**Fat Area**

Visceral and subcutaneous fat areas were measured by electron beam tomography (EBT) with a GE Imatron-150 EBT scanner (GE Imatron, South San Francisco, CA). Participants were examined in the supine position with both arms stretched above the head. The scan was performed at the L4-L5 vertebrae level using a scout image of the body to establish the precise scanning position (DeNino et al., 2001; Poehlman, Dvorak, DeNino, Brochu, & Ades, 2000). This position encompasses the largest percentage of fat in the body and best allows differentiation of visceral from subcutaneous fat (Borkan et al., 1982). A single 3- or 6-mm slice was taken during suspended respiration after a normal expiration. After the acquisition, the scan was transferred to an AccuImage image analysis workstation where abdominal adipose tissue areas were measured using the AccuAnalyzer module. Total abdominal fat was calculated by delineating the body surface with a stylus and then computing the adipose tissue surfaces with an attenuation range of –190 to –30 Hounsfield units (DeNino et al., 2001; Poehlman et al., 2000). The visceral fat area was quantified by delineating with a stylus the abdominal cavity at the internal-most aspect of the abdominal wall (transversalis fascia) and the posterior aspect of the vertebral body. The subcutaneous fat area was calculated by subtracting the visceral area from the total area. Determination of visceral fat from a single scan at L4-L5 is highly correlated to total visceral fat volume in both genders (Kvist, Chowdhury, Grangard, Tylen, & Sjostrom, 1988). Excellent reproducibility of fat measurements using this technique was shown by a high correlation between duplicate measurements ($r = .99$) and by small precision errors: 1.2% for total, 1.9% for subcutaneous, and 3.9% visceral (Thaete, Colberg, Burke, & Kelley, 1995).

**Fat Mass**

Total, trunk, and limb fat and fat-free masses were determined from the whole-body dual-energy X-ray absorptiometry (DXA) scan, which uses a three-compartment model: (a) whole-body fat mass, (b) whole-body bone-free lean tissue mass, and (c) whole-body bone mass. Regions of interest were delineated using a stylus. At tissue thickness ranging from 5 to 25 cm, errors in measurement of fat for whole-body scans were less than 3% (Blake, Wahner, & Fogelman, 1999). The standard errors for the measurement of body composition are 1.9 kg for fat mass and 2.7 kg for lean body mass (Blake et al., 1999). The short-term precision (coefficient of variation %) of DXA in adults has been reported as 4.9% for fat, 4.6% for fat mass, and 1.5% for lean body mass (Blake et al., 1999). Although not yet a gold standard, there is good agreement between DXA measurement of body composition and other methods, such as underwater weighing and densitometry (Pritchard et al., 1993; Wang et al., 1996; Wellens et al., 1994).

**Lipid Levels**

Lipid levels were measured from fasting sera by standard clinical laboratory procedures. Analyses were performed in a Clinical Laboratory Improvement Amendments–certified laboratory. The triglyceride levels were determined using the glycerol kinase/peroxidase technique. High-density lipoprotein and low-density lipoprotein (LDL) cholesterol were determined using dextran sulfate precipitation oxidase and enzymatic techniques, respectively.

**Insulin Sensitivity**

The homeostatic model assessment (HOMA; Matthews et al., 1985) was used to yield an estimate of insulin sensitivity from one-time fasting plasma insulin (determined via chemiluminescent immunosay) and glucose (determined via hexokinase spectrophotometry) concentrations. The predictions used in the model arise from experimental data in humans and animals. The equation for percentage sensitivity is

$$S\% = \frac{FPI \times FPG}{22.5}$$

and for percentage β-cell function is

$$\beta\% = \frac{20 \times FPI}{FPG - 3.5}$$

where FPI is fasting plasma insulin concentration (mU/L) and FPG is fasting plasma glucose (mmol/L). Strong correlations have been demonstrated among the HOMA, the hyperinsulinemic-euglycemic clamp ($R^2 = .82$ .88; Bonora et al., 2000; Matthews et al., 1985), and the minimal model assessment ($r = .7$; Garcia-Estevez, Araujo-Vilar, Fiestras-Janiero, Saavedra-Gonzalez, & Cabezas-Cerrato, 2003). The HOMA has been shown to be sensitive to change and able to detect insulin sensitivity longitudinally (Wallace, Levy, & Matthews, 2004).
Results

A total of 9 participants were recruited; however, only 5 completed the 16-week intervention and had preintervention and postintervention data available for analysis. Demographic and HIV disease-related characteristics for all recruited participants are shown in Table 3. The mean number of exercise sessions attended by participants who completed the intervention was 43 ± 3.7. All participants were able to exercise at the prescribed duration and intensity without difficulty. Participants who completed the intervention had significantly higher baseline total cholesterol than those who did not complete it (242.8 ± 54.3 vs. 178.8 ± 39.4 mg/dL, respectively). Completers and noncompleters did not significantly differ on other baseline measurements (data not shown). Of those who did not complete the intervention, 2 were lost to follow-up, 1 could not continue because of peripheral neuropathy, and 1 found the time commitment too burdensome.

Mean improvement in aerobic capacity (VO$_{2\text{max}}$) was 3.4 ± 3.2 ml/kg/min (from 31.1 ± 5.9 to 34.5 ± 6.8 ml/kg/min; $z = -1.75$, $p = .08$), and mean increase in strength was 227.6 ± 84.8 lb, which represents a mean sum of increases in 1-RM for all seven resistance exercises (from 1,254 ± 341.8 to 1,482.5 ± 299.3 lb; $z = -2.02$, $p = .04$). Mean and percentage changes from preintervention to postintervention in outcome measures along with results from paired Wilcoxon rank sum tests are found in Table 4.

Discussion

Participants entered the study in an aerobically deconditioned state that improved with training, as evidenced by the increase in aerobic capacity. Strength was significantly improved over the course of the 16-week intervention, as shown by the mean sum increase in 1-RM. The only statistically significant outcome measure changes were a decrease in total body and trunk fat as measured by DXA. These two variables are highly correlated, and the loss of trunk fat likely accounts for the significance in loss of total fat.

Given the pilot status of these data, the small sample size, and lack of control, definitive conclusions cannot be drawn. However, some intriguing trends were noted that support further testing of exercise in this patient population. In addition, particular methodological issues emerged that can and should be addressed in future testing.

### Table 3. Sample Demographics and HIV Disease-Related Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Completers ($n = 5$)</th>
<th>Noncompleters ($n = 4$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Age (years)</td>
<td>44 ± 3.8</td>
<td>40.5 ± 7.1</td>
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<tr>
<td>Race</td>
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<td></td>
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<tr>
<td>African American</td>
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<td>1</td>
</tr>
<tr>
<td>Caucasian</td>
<td>3</td>
<td>3</td>
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<tr>
<td>HIV risk factors</td>
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<td></td>
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<tr>
<td>MSM</td>
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<td>3</td>
</tr>
<tr>
<td>Heterosexual</td>
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<td>0</td>
</tr>
<tr>
<td>IDU</td>
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<td>1</td>
</tr>
<tr>
<td>Current or past smoker</td>
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<td>2</td>
</tr>
<tr>
<td>Duration of HIV infection (years)</td>
<td>6.4 ± 2.7</td>
<td>11 ± 3.8</td>
</tr>
<tr>
<td>CD4+ cell number (cells/mm$^3$)</td>
<td>505 ± 296.5</td>
<td>538 ± 380.6</td>
</tr>
<tr>
<td>Viral load</td>
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<td></td>
</tr>
<tr>
<td>Undetectable</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Detectable</td>
<td>2$^a$</td>
<td>2$^b$</td>
</tr>
<tr>
<td>HAART regimen</td>
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<td></td>
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<tr>
<td>NRTI, PI</td>
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<td>2</td>
</tr>
<tr>
<td>NRTI, NNRTI</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>NRTI, NNRTI, PI</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

NOTE: Data are mean ± standard deviation for continuous variables and frequencies for categorical variables. MSM = men who have sex with men; IDU = injecting drug user; HAART = highly active antiretroviral therapy; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor.

a. Actual values were 60 and 1,500 cells/mm$^3$.
b. Actual values were 55 and 1,000 cells/mm$^3$. 

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The significant loss of trunk fat accompanied by the trend for increased total and limb lean tissue suggests that exercise training may be effective in reducing abdominal adiposity and increasing muscle mass, which may impart greater whole-body insulin sensitivity (Buemann & Tremblay, 1996; Simoneau, Colberg, Thaete, & Kelley, 1995). Previous pilot work of combined endurance and resistance training produced a similar decrease in trunk fat (Roubenoff, Weiss, et al., 1999).

The current data failed to support an effect of exercise on the distribution of fat in the abdominal depots. No changes were noted in the area of visceral fat; however, a small but nonsignificant decrease was found for the subcutaneous fat area. The single previous published study that examined changes in abdominal visceral and subcutaneous fat area (measured with computed tomography [CT] scan) as a result of combined endurance and resistance training in an HIV sample showed significantly decreased visceral fat area without changes in the area of subcutaneous fat (Thoni et al., 2002). In repeated-measures design, precise scanning position is critical to ensuring accuracy of the comparisons across time points. Although we used the L4-L5 vertebrae as our landmark for scanning, the radically different within-subject slice circumferences suggest that greater precision in scanning protocol was warranted. Therefore, we chose to report the percentage of fat relative to the entire area of the slice as a means to standardize across time points. As such, our results should be interpreted cautiously.

The mean baseline values were elevated for total and LDL cholesterol and triglycerides. Although not statistically significant, a 59 mg/dL drop in triglyceride level may be clinically significant. Decreases in triglycerides have been shown to occur in previous small studies of resistance (Yarasheski et al., 2001), endurance (Thoni et al., 2002), and combination (Jones et al., 2001) exercise in HIV samples. A small, nonsignificant decrease was noted in total and LDL cholesterol. Previous research testing endurance training with and without a resistance-training component reported significant reductions in total cholesterol, LDL cholesterol, or both (Jones et al., 2001; Thoni et al., 2002).

In terms of insulin sensitivity, on average, the sample had normal percentage sensitivity and β-cell function at baseline. Therefore, it would not be expected that insulin sensitivity would improve with exercise. However, the mean percentage sensitivity and β-cell function actually decreased with exercise, although not significantly. Only 1 participant had percentage insulin sensitivity and β-cell values that indicated some level of insulin resistance. This individual responded in the anticipated direction and achieved normal percentage sensitivity and β-cell function.
postintervention. The only other study (Thoni et al., 2002) to assess changes in insulin sensitivity with exercise in an HIV sample (also a small pilot of 9 participants) using a HOMA model likewise found no significant changes. Abundant evidence suggests that the independent effects of exercise (i.e., without concomitant weight loss) are related to the last bout of exercise. Therefore, standardized timing of insulin and glucose levels relative to the last bout of exercise is critical for interpretation of results. Levels of glucose and insulin were drawn within a week of the last exercise session. This timing schema was not precise enough to ensure accurate assessment of changes in insulin sensitivity.

In conclusion, to date, the effect of endurance and resistance exercise on HIV metabolic abnormalities has been studied in mostly small, uncontrolled studies, including this pilot study. Larger randomized trials, such as the one conducted by Smith and colleagues (2001), used manual anthropomorphic measures to show loss of central fat; it is therefore difficult to compare results to studies using DXA or CT (or magnetic resonance imaging) adipose measurement. A series of reports from Driscoll and colleagues (Driscoll, Meininger, Lareau, et al., 2004; Driscoll, Meininger, Ljungquist, et al., 2004) suggests that resistance exercise and combination endurance/resistance exercise along with metformin is more effective at enhancing insulin sensitivity than metformin alone in HAART-treated individuals with hyperinsulinemia and fat redistribution. Although informative, these data do not address the role that exercise may play in preventing the need for pharmacological intervention. No fully powered randomized controlled trial of exercise versus usual activity has been conducted in the post-HAART era that examines lipids, insulin sensitivity, or radiographically measured abdominal adiposity. Such studies are urgently needed, as the current piecemeal evidence is insufficient to provide recommendations.

We suggest that investigators conducting future clinical trials of exercise in HIV consider the following. Participants need to be well classified in terms of lipid levels, insulin sensitivity, and fat redistribution at study entry. Given the diversity of expression of metabolic abnormalities in the HIV population, it is unlikely that the full constellation of abnormalities will be found in all participants. Therefore, specific inclusion/exclusion criteria related to the variable of interest or exclusion from analysis of participants with normal baseline values for the variable of interest may be warranted to avoid a statistical floor/ceiling effect. Ideally, randomized trials should contain various dose-response arms with various frequencies, intensities, and durations of endurance or resistance exercise or both. Previously tested frequencies, intensities, and durations are based on data from other populations and may or may not be appropriate in the context of HIV disease. Finally, timing of outcome measures is crucial. Given the acute metabolic effects of exercise on metabolic parameters, it may be prudent to measure lipid levels and insulin sensitivity precisely at 12 to 15 hr after the last bout of exercise and again 72 hr later. Data from both time points may be informative and will provide information related to acute exercise effects as well as sustained effects that might occur because of such phenomena as muscle hypertrophy.

References


