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## Exercise training augments the peripheral insulin-sensitizing effects of pioglitazone in HIV-infected adults with insulin resistance and central adiposity

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**Yarasheski KE, Cade WT, Overton ET, Mondy KE, Hubert S, Laciny E, Bopp C, Lassa-Claxton S, Reeds DN.** Exercise training augments the peripheral insulin-sensitizing effects of pioglitazone in HIV-infected adults with insulin resistance and central adiposity. *Am J Physiol Endocrinol Metab* 300: E243–E251, 2011. First published October 19, 2010; doi:10.1152/ajpendo.00468.2010.—The prevalence and incidence of insulin resistance and type 2 diabetes mellitus (DM) are higher in people treated for human immunodeficiency virus-1 (HIV) infection than in the general population. Identifying safe and effective interventions is a high priority. We evaluated whether the peroxisome proliferator-activated receptor- $\gamma$  agonist pioglitazone with exercise training improves central and peripheral insulin sensitivity more than pioglitazone alone in HIV-infected adults with insulin resistance and central adiposity. Forty-four HIV-infected adults with baseline insulin resistance and central adiposity were randomly assigned to 4 mo of pioglitazone (30 mg/day) with or without supervised, progressive aerobic, and resistance exercise training (1.5–2 h/day, 3 days/wk). The hyperinsulinemic euglycemic clamp was used to evaluate alterations in central and peripheral insulin sensitivity. Thirty-nine participants completed the study. Hepatic insulin sensitivity improved similarly in both groups. Exercise training augmented the beneficial effects of pioglitazone on peripheral insulin sensitivity. Greater improvements in peripheral insulin sensitivity were associated with reductions in total body and limb adipose content rather than increases in limb adiposity or pioglitazone-induced increases in adiponectin concentration. We conclude that supplementing pioglitazone with increased physical activity improved insulin sensitivity more effectively than pioglitazone alone in HIV-infected adults with insulin resistance and central adiposity. Pioglitazone alone did not significantly increase limb adipose content. Potential cardiovascular benefits of these interventions in HIV need investigation.

human immunodeficiency virus-1; cardiovascular disease risk factors; diabetes; chronic inflammation; metabolic complications; physical activity

DESPITE ADVANCES IN COMBINATION antiretroviral therapy (cART) that reduce morbidity and mortality, insulin resistance and type 2 diabetes mellitus (DM) are common cardiovascular disease (CVD) risk factors among people living with human immunodeficiency virus-1 (HIV). In cross-sectional comparisons adjusted for age and body mass index, DM prevalence was 4.6

times higher and DM incidence was 4.1 times higher in HIV-infected men than in HIV-seronegative men (6). In age-stratified analyses, DM prevalence was 11% in HIV-infected men <40 yr old and 18% in those  $\geq$ 40 yr old, whereas corresponding DM prevalence rates in HIV-seronegative men were 3 and 13%, respectively (27). In HIV, insulin resistance and DM are common and important CVD risk factors for which few safe and effective treatments exist.

CVD is a leading cause of death in HIV-infected adults (11). HIV-infected adults have a twofold higher prevalence of cardiovascular events than the general population (56). Recent estimates suggest that the risk of death from DM is 6.4-fold higher in AIDS patients than in the general population. Clearly, safe and effective prevention and treatment strategies for insulin resistance and DM are a high priority and may substantially reduce cardiovascular morbidity and mortality among HIV infected people.

Exercise training and thiazolidinediones (TZDs; rosiglitazone, pioglitazone) represent potential treatments for insulin resistance and DM in HIV-infected people. TZDs are synthetic ligand activators of the nuclear transcription factor peroxisome proliferator-activated receptor- $\gamma$  (PPAR $\gamma$ ) and potent insulin sensitizers. PPAR $\gamma$  is the most abundant adipose PPAR isoform, where it regulates lipid and glucose metabolism. PPAR $\gamma$  activation [dephosphorylation (12)] increases circulating levels of the insulin sensitizer adiponectin (53), and several cART drugs downregulate adipocyte PPAR $\gamma$  gene and protein expression (15, 35). We tested whether pioglitazone-induced activation of PPAR $\gamma$  improves insulin sensitivity in HIV-infected adults taking cART.

The benefits of a physically active lifestyle for controlling CVD risk factors (insulin resistance, diabetes, dyslipidemia, hypertension, central adiposity, autonomic dysfunction, low aerobic capacity) and CVD progression are well established (4, 26). Strenuous exercise is not required; moderate-intensity physical activity reduces CVD and DM risk (4, 13, 19, 26, 37). Many HIV-infected adults are sedentary, have low aerobic capacity (7), develop CVD risk factors, and live long enough to develop atherosclerosis (5, 18, 36, 45). HIV-infected people with DM and other CVD risk factors are well suited to benefit from a physically active lifestyle (31). Interestingly, exercise training activates PPAR $\delta$ , the most abundant PPAR isoform in muscle. Exercise-induced muscle PPAR $\delta$  and adenosine 5'-monophosphate-activated protein kinase (AMPK) activation are associated with improved fatty acid transport and oxidation, improved glucose uptake/insulin sensitivity, and enhanced mitochondrial function in DM after low-intensity aerobic exercise training (19, 29).

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Pioglitazone and exercise training mediate their insulin-sensitizing actions through two different transcription factors in adipose and muscle tissue (PPAR $\gamma$  and PPAR $\delta$ ). cART disrupts PPAR $\gamma$  activation in insulin-sensitive tissues in HIV-infected people. Therefore, we hypothesized that pioglitazone treatment would improve peripheral insulin sensitivity and that combined pioglitazone and exercise training would further enhance peripheral insulin sensitivity in HIV-infected adults with baseline insulin resistance and central adiposity.

## METHODS

### Participants

HIV-infected men and women (18–60 yr old) were recruited from the AIDS Clinical Trials Unit, the Infectious Diseases Clinic, and the Volunteers for Health Program at Washington University School of Medicine (Table 1). None of the participants had an AIDS diagnosis. This was a prospective, two-group, random assignment study. The purpose was to determine the effectiveness of 4 mo of pioglitazone (pio; 30 mg/day) or pioglitazone plus exercise (pio + ex) training on several metabolic, endocrine, anthropomorphic, and safety parameters in HIV-infected people with baseline insulin resistance/impaired glucose tolerance and central adiposity. Insulin resistance/impaired glucose tolerance was defined as fasting glucose of 5.6–7.0 mM or glucose values of 7.8–11.1 mM 2 h after ingestion of a 75-g glucose beverage (ADA criteria) or fasting insulin concentration  $>72$  pM ( $>12$   $\mu$ U/ml). Central adiposity was defined as trunk/limb adipose mass  $>1.1$  (men) or  $>0.9$  (women), measured using dual-energy X-ray absorptiometry (DEXA). The primary outcome was peripheral insulin sensitivity; glucose disposal rate was measured during a 5-h hyperinsulinemic euglycemic clamp that included a [6,6- $^2$ H $_2$ ]glucose tracer to quantify endogenous glucose production rate. Secondary outcomes included body fat distribution, abdominal subcutaneous and visceral adipose volume, liver lipid content, thigh muscle volume, regional bone mineral density (BMD), fasting serum lipid/lipoprotein concentrations, and selected safety parameters (liver enzymes, hematocrit, hemoglobin). The Human Research Protection Office at Washington University School of Medicine approved the study, and all participants provided verbal and written informed consent before participating. The study was registered with ClinicalTrials.gov (NCT no. 00639457).

Table 1. Participants' baseline characteristics

	Pioglitazone	Pio + Ex Training	P Value
n (%Women)	20 (15%)	19 (11%)	0.77
Ethnicity (C/AA/H)	11/8/1	14/5/0	0.17
Age, yr	44 $\pm$ 2	46 $\pm$ 2	0.56
Years known HIV +	11 $\pm$ 1	13 $\pm$ 1	0.39
CD4 count, cells/ $\mu$ l	586 $\pm$ 47	558 $\pm$ 36	0.65
Plasma HIV RNA	100% Und	95% Und	0.33
BMI, kg/m $^2$	29.1 $\pm$ 1.2	28.3 $\pm$ 1.1	0.62
Current anti-HIV medications (%participants)			
Zidovudine	41%	29%	0.46
Stavudine	5%	0%	0.38
Other NRTI	100%	88%	0.10
Tenofovir	55%	65%	0.53
NNRTI	27%	18%	0.48
Efavirenz	14%	24%	0.43
Boosted PI	64%	47%	0.32
Unboosted PI	9%	12%	0.79

Values are means  $\pm$  SE. Pio + Ex, pioglitazone plus exercise; C, Caucasian; AA, African American; H, Hispanic; BMI, body mass index; Und, plasma HIV RNA ( $<400$  copies/ml); NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Before enrollment, volunteers received a physical examination, including a medical history, fasting blood chemistry, lipid/lipoprotein and serum endocrine profile, a 2-h, 75-g oral glucose tolerance test with insulin monitoring, resting blood pressures ( $3\times$  at rest), urine drug and pregnancy screens, and plasma HIV RNA quantitation (Roche Amplicor HIV-1 Monitor; Roche Diagnostics, Indianapolis, IN). Volunteers were excluded if they were taking medications or dietary supplements that could affect metabolism ( $\beta$ -blocker,  $\beta$ -agonist, Ca $^{2+}$  channel blocker, corticosteroid) or had a neuromuscular (severe peripheral neuropathy) or other disorders that might affect metabolism or ability to exercise. All participants consumed less than three alcohol-containing beverages per week, did not have active hepatitis C or B infection, were not using recreational drugs (except marijuana) for 6 mo prior to enrollment, and were weight stable ( $<2\%$  weight change in the 3 mo prior to the study). None of the subjects took anabolic agents or appetite stimulants for  $\geq 6$  mo prior to study. None of the subjects participated regularly in physical activities that would constitute exercise training.

### Interventions

Participants were randomly assigned (1:1) to 4 mo of pioglitazone with or without exercise training.

### Pioglitazone

The research pharmacist distributed a 1-mo supply of pioglitazone tablets (30 mg/day) to each participant during each monthly visit. Participants were instructed to take one tablet each day with their lunch meal. Anti-HIV medications are typically taken in the morning, so to minimize potential drug interactions, pioglitazone was taken later in the day. For the 1st month, participants used a glucometer to document their random fasting blood glucose concentrations to protect against hypoglycemia.

### Exercise Training

The 4-mo exercise training program consisted of 1.5–2 h/day, 3 days/wk, of supervised, progressive, combined aerobic conditioning and resistance training. A certified exercise trainer prescribed and supervised each exercise session. Exercise was conducted at an indoor exercise facility on the Washington University Medical School campus. Exercise frequency, intensity, duration, and mode of activity for improving cardiorespiratory fitness, muscular strength, and endurance were prescribed as recommended (26, 37). Aerobic exercise intensity was based on a percent predicted maximum heart rate (HR). The target HR range during aerobic exercise was 50–85% HR reserve (i.e., moderate to high intensity). During exercise, HR and time at the target HR were monitored by outfitting each participant with a battery-operated HR monitor (Polar, Lake Success, NY) that signaled an alarm if the target HR range was not maintained during exercise. HR and time data were stored in the monitor and documented daily to verify adherence and response to the exercise prescription. The trainer progressively increased the exercise intensity as the participant adapted. Aerobic exercise involved stationary cycling, treadmill walk/jogging, stair-stepper climbing, or elliptical training device. The exercise program was individualized to each participant's baseline physical fitness level.

The resistance exercise component consisted of four upper and three lower body exercises and followed the aerobic exercise session. Baseline voluntary maximum strength (1 repetition maximum) was measured during the first three to four exercise sessions on each of the exercise machines. Initially, the progressive resistance training program consisted of one to two sets of each exercise while lifting a weight that caused muscle fatigue/failure after eight repetitions. The trainer monitored the participant's exercise response daily, and when the participant comfortably lifted the weight for 12 repetitions on any exercise, the weight (intensity) was increased by an amount ( $\sim 10\%$ )

that caused the muscle group to fatigue/fail after eight repetitions. This progressive eight- to 12-repetition cycle was repeated for each exercise over the 4-mo period.

#### Dietary Control

Participants were admitted to the Clinical Research Unit (CRU) for a 24-h period. For 3 days prior to admission and on the evening before the hyperinsulinemic euglycemic clamp, they consumed a standard weight-maintaining diet that contained adequate amounts of energy and macronutrients:  $\geq 250$  g carbohydrate/day and  $\sim 12\%$  protein,  $\sim 55\%$  carbohydrate, and  $\sim 33\%$  fat calories. Compliance with these guidelines was assessed using 3-day food recall records that were reviewed by a research dietician. This was done to reduce the effects of prior diet on glucose metabolism quantified during the clamp. At *week 16*, the clamp was conducted 36–48 h after the last exercise training session to minimize the acute effects of the last exercise session, and the final dose of pioglitazone was taken on the morning of the clamp. During the CRU admission, participants abstained from exercise, nicotine, caffeine, or alcohol ingestion.

#### Measurements

**Hyperinsulinemic euglycemic clamp.** After an overnight fast (from 2000), a catheter was inserted into an antecubital vein (0530) and used to administer  $[6,6\text{-}^2\text{H}_2]$ glucose, insulin, and sterile 20% dextrose solution (Baxter Healthcare, Deerfield, IL). A second catheter was inserted into a vein on the contralateral hand that was heated ( $55^\circ\text{C}$ ) using a thermostatically controlled Plexiglas chamber to obtain arterialized venous blood samples. At 0700, a primed ( $11.0 \mu\text{mol/kg}$ ), constant ( $11.0 \mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ) intravenous infusion of  $[6,6\text{-}^2\text{H}_2]$ glucose (98% isotopic purity; Cambridge Isotope Laboratories; Andover, MA) was started. The clamp was conducted in two-stages, 1) a 2-h baseline period, during which only  $[6,6\text{-}^2\text{H}_2]$ glucose was infused intravenously and 5-ml arterialized venous blood samples were collected at  $-5$ , 0, 90, 100, 110, and 120 min for quantifying  $[^2\text{H}_2]$ glucose abundance, glucose, and insulin concentrations, followed by 2) a 3-h period during which the  $[6,6\text{-}^2\text{H}_2]$ glucose tracer infusion was maintained, a primed ( $120 \text{mU}\cdot\text{m}^{-2}\cdot\text{min}^{-1} \times 5 \text{min}$ ,  $60 \text{mU}\cdot\text{m}^{-2}\cdot\text{min}^{-1} \times 5 \text{min}$ ), constant ( $30 \text{mU}\cdot\text{m}^{-2}\cdot\text{min}^{-1}$ ) infusion of regular human insulin (Eli Lilly, Indianapolis, IN) was started, and a variable rate infusion of dextrose {spiked with 1.5%  $[6,6\text{-}^2\text{H}_2]$ glucose (wt/wt)} was used to maintain blood glucose concentration at 5.6 mM. Plasma glucose concentration was quantified ( $\sim 1$  ml of blood) every 10 min during the clamp to prevent against hypoglycemia and used to adjust the variable rate dextrose infusion. At the end of *stage 2*, 5-ml arterialized venous blood samples were collected at 150, 160, 170, and 180 min for quantifying  $[^2\text{H}_2]$ glucose enrichment, glucose, and insulin concentrations.

**Body composition assessment.** Whole body fat, fat-free mass (FFM), and hip (total) and lumbar spine ( $L_1\text{--}L_4$ ) bone mineral densities were quantified using a Hologic Discovery fan beam, multi-element array DEXA. A certified technologist using Hologic software (version 12.4) processed the images. Abdominal subcutaneous (SAT) and visceral adipose tissue (VAT) volumes and right and left thigh muscle and SATs were visualized using  $^1\text{H}$ -magnetic resonance imaging (1.5-T whole body Siemens Sonata; Siemens Medical Systems, Erlangen, Germany) and their volumes quantified using Analyze software (Mayo Clinic, Rochester, MN) as described (1). Intrahepatic lipid content (%water signal) was quantified using  $^1\text{H}$ -magnetic resonance spectroscopy (1.5-T whole body Siemens Magnetom Vision system) as described (47).

**Plasma/serum analyses.** Plasma glucose concentration was quantified using an automated glucose analyzer (Yellow Springs Instruments, Yellow Springs, OH). Plasma insulin concentrations were quantified using a chemiluminescent immunometric method (Immupoint; Siemens, Los Angeles, CA). The insulin assay range is 12–1,800 pM, and the interassay coefficient of variation is 4% in the low (63

pM) and high insulin concentration range (331 pM). Fasting serum lipid/lipoprotein levels were quantified as described previously (59). Direct LDL cholesterol levels were measured when fasting serum triglycerides were  $>4.5$  mM. Plasma total adiponectin concentrations were quantified using a commercial ELISA kit (Invitrogen, Camarillo, CA). The lower limit of quantitation was  $0.6 \pm 0.3 \mu\text{g/ml}$ . At low (2  $\mu\text{g/ml}$ ), moderate (4  $\mu\text{g/ml}$ ), and high (16  $\mu\text{g/ml}$ ) concentrations the intra-assay variability was 5, 3, and 2%, and the interassay variability was 7, 6, and 2%, respectively.

Plasma  $[^2\text{H}_2]$ glucose tracer/tracee ratios (TTR) were quantified using capillary gas chromatography-mass spectrometry (GC-MS; Agilent 6890N gas chromatograph and Agilent 5973N mass selective detector) (50). Plasma (200  $\mu\text{l}$ ) proteins were precipitated with cold acetone (200  $\mu\text{l}$ ), the aqueous phase was dried under  $\text{N}_2$  gas (Speed-Vac; Savant Instruments, Farmingdale, NY), and the penta-acetate derivative was formed.  $[^2\text{H}_2]$ glucose enrichment was quantified using GC-positive chemical ionization-MS with selected ion monitoring ( $m/z$  333 and 331) and used to calculate TTR as described (10). The GC-MS instrument response was calibrated using gravimetric standards of known  $[^2\text{H}]$ glucose enrichment.

#### Calculations

Plasma glucose rate of appearance ( $R_a$ ; endogenous glucose production) was calculated by dividing the total  $[6,6\text{-}^2\text{H}_2]$ glucose tracer infusion rate by the average TTR measured during the last 30 min of each stage of the clamp and subtracting the tracer infusion rate. Basal hepatic insulin sensitivity was calculated as the reciprocal of the hepatic insulin resistance index [ $100/(\text{endogenous glucose } R_a \text{ in } \mu\text{mol/min} \times \text{fasting insulin concentration in } \mu\text{U/ml})$ ] (28). Glucose rate of disappearance ( $R_d$ ; peripheral glucose disposal) was calculated as the sum of endogenous glucose  $R_a$  plus infused dextrose. Kinetic rates were expressed per kg FFM. Right and left thigh muscle and subcutaneous adipose volumes were measured separately, averaged, and reported as a single value. The homeostasis model assessment insulin resistance index (HOMA-IR) was calculated as described (38).

#### Statistical Analyses

Baseline descriptive characteristics (i.e., sex, ethnicity, HIV RNA below detection, anti-HIV medication use) were compared using a Mann-Whitney  $U$ -test, whereas ratio level descriptive parameters (age, BMI, hormone levels) were compared using a two-sided  $t$ -test. Within-group comparisons (baseline vs. postintervention) were made using a two-sided paired  $t$ -test. Change from baseline to postintervention values for each parameter was calculated and compared between groups using a two-sided  $t$ -test and a Mann-Whitney  $U$ -test. The primary findings and conclusions were the same regardless of the statistical test used, so the between-group  $t$ -test values are reported. Univariate associations between continuous variables were evaluated using Spearman regression analysis.  $P < 0.05$  was considered statistically significant.

## RESULTS

Forty-four eligible volunteers agreed to enroll; 39 completed the 4-mo intervention and all testing (pio,  $n = 20$ ; pio + ex,  $n = 19$ ; Table 1). One pio participant dropped out (noncompliant), and one pio participant was discontinued (positive drug screen at *week 2*). Three pio + ex participants dropped out (noncompliant for personal reasons). Women represented 13% and ethnic minorities 36% of the participants. VAT and SAT volumes were not different between groups but relatively large, indicating that both groups had central adiposity (Table 2). Average HOMA-IR ( $>3.0$ ) indicated that both groups were insulin resistant at baseline (Table 3). At baseline, the groups were matched for demographic, physical, endocrine, immune,

Table 2. Baseline and postintervention total and regional body composition parameters

Parameter	Pio			Pio + Ex Training			Between-Group P Value
	Baseline	Post	Change	Baseline	Post	Change	
Weight, kg	90.1 ± 4.1	90.6 ± 4.2	0.5 ± 0.7	88.7 ± 3.7	88.2 ± 3.5	-0.5 ± 1.0	0.39
Fat mass, kg	24.6 ± 2.6	25.3 ± 2.6	0.6 ± 0.5	23.5 ± 2.3	22.6 ± 2.4	-0.9 ± 0.6	0.14
Fat-free mass, kg	65.5 ± 2.1	65.3 ± 2.2	-0.1 ± 0.4	65.2 ± 2.0	65.6 ± 1.8	0.4 ± 0.7	0.57
Trunk fat mass, kg	15.0 ± 1.5	15.4 ± 1.4	0.3 ± 0.3	14.4 ± 1.5	13.6 ± 1.5	-0.8 ± 0.4	0.08
Limb fat mass, kg	8.6 ± 1.2	8.8 ± 1.3	0.3 ± 0.2	8.0 ± 1.0	7.9 ± 1.1	-0.1 ± 0.2	0.14
VAT, cm <sup>3</sup>	1,933 ± 150	1,970 ± 164	37 ± 47	1,890 ± 217	1,746 ± 177	-144 ± 79	0.09
SAT, cm <sup>3</sup>	2,101 ± 293	2,164 ± 286	63 ± 52	1,877 ± 197	1,905 ± 230	28 ± 74	0.70
Liver lipid, %	12.1 ± 2.0	10.7 ± 2.4	-1.5 ± 1.3	8.0 ± 1.7	5.5 ± 0.8	-2.6 ± 1.4	0.095
Right and left thigh subcutaneous fat, cm <sup>3</sup>	37 ± 9	38 ± 9	1 ± 1	32 ± 7	31 ± 8	-1 ± 2	0.64
Right and left thigh muscle, cm <sup>3</sup>	117 ± 5	115 ± 5	-2 ± 1	113 ± 4	118 ± 5	5 ± 2	0.0009
Total hip BMD, g/cm <sup>3</sup>	0.99 ± 0.04	0.96 ± 0.04	-0.03 ± 0.03	0.98 ± 0.02	0.98 ± 0.02	0.00 ± 0.00	0.69
Hip z-score	-0.07 ± 0.25	-0.13 ± 0.24	-0.07 ± 0.07	-0.19 ± 0.12	-0.21 ± 0.13	-0.01 ± 0.03	0.68
Lumbar spine BMD, g/cm <sup>3</sup>	1.03 ± 0.03	1.04 ± 0.04	0.01 ± 0.01	1.06 ± 0.03	1.06 ± 0.03	0.00 ± 0.01	0.20
Lumbar spine z-score	-0.45 ± 0.34	-0.40 ± 0.34	0.05 ± 0.05	-0.19 ± 0.21	-0.26 ± 0.22	-0.07 ± 0.05	0.31

Values are means ± SE; VAT, visceral adipose tissue volume; SAT, abdominal subcutaneous adipose tissue volume; BMD, bone mineral density.

Table 3. Baseline and postintervention blood metabolite, hormone, and immune parameters

Parameter	Pio			Pio + Ex Training			Between-Group P Value
	Baseline	Post	Change	Baseline	Post	Change	
Triglycerides, mM	2.3 ± 0.3	2.5 ± 0.3	0.2 ± 0.2	2.1 ± 0.4	1.8 ± 0.2	-0.3 ± 0.4	0.61
Total cholesterol, mM	4.9 ± 0.2	4.6 ± 0.2	-0.3 ± 0.2	4.7 ± 0.2	4.5 ± 0.2	-0.2 ± 0.2	0.54
LDL cholesterol, mM	2.8 ± 0.2	2.5 ± 0.1	-0.3 ± 0.2	2.7 ± 0.2	2.6 ± 0.2	-0.1 ± 0.2	0.54
HDL cholesterol, mM	0.99 ± 0.05	0.98 ± 0.05	-0.01 ± 0.03	1.06 ± 0.05	1.09 ± 0.05	0.03 ± 0.06	0.96
CD4+ T cell count, cells/ $\mu$ l	586 ± 47	601 ± 51	15 ± 22	558 ± 36	527 ± 35	-31 ± 23	0.12
ALT, U/l	38 ± 7	39 ± 8	1 ± 5	34 ± 6	32 ± 6	-2 ± 2	0.45
AST, U/l	34 ± 7	30 ± 4	-4 ± 4	27 ± 4	27 ± 3	0 ± 2	0.70
Alkaline phosphatase, U/l	80 ± 6	72 ± 5	-8 ± 3	83 ± 6	76 ± 6	-6 ± 3	0.06
Hematocrit, %	39.9 ± 0.7	39.6 ± 0.7	-0.3 ± 0.3	40.7 ± 1.4	39.7 ± 1.3	-1.0 ± 1.0	0.12
Hemoglobin, g/l	13.8 ± 0.3	13.7 ± 0.3	-0.1 ± 0.1	13.8 ± 0.5	13.6 ± 0.4	-0.2 ± 0.2	0.24
Adiponectin, $\mu$ g/ml	4.7 ± 0.8	7.0 ± 0.7	2.3 ± 0.5	4.8 ± 0.8	6.5 ± 0.9	1.7 ± 0.5	0.002
HOMA-IR	4.5 ± 0.6	3.7 ± 0.5	-0.8 ± 0.3	3.4 ± 0.4	2.6 ± 0.4	-0.8 ± 0.2	0.0004
Total testosterone, ng/ml	436 ± 22	432 ± 33	6 ± 20	468 ± 51	506 ± 55	38 ± 50	0.36
TSH, mU/l	1.93 ± 0.31	ND		1.51 ± 0.19	ND		

Values are means ± SE; ALT, alanine transaminase; AST, aspartate transaminase; HOMA-IR, homeostasis model assessment of insulin resistance; ND, not done.

and virologic parameters (Table 1). One participant (pio + ex) was naïve to cART, and one participant (pio) was taking stavudine, but the percentage of participants using nucleoside reverse transcriptase inhibitors (thymidine analog and others) was similar between groups (Table 1). The percentage of participants using nonnucleoside reverse transcriptase inhibitors and protease inhibitors (ritonavir-boosted or unboosted) was similar between the groups. No medication changes occurred during the study.

### Exercise Training

During the 4-mo intervention, participants attended a median 44 (range 26–50) exercise sessions (92% compliance), completed a median 22 h (10–37 h) of aerobic exercise in their target HR zone, and expended a median 97 J (34–149 J) of energy during aerobic exercise. Median rate of energy expenditure during aerobic exercise was 61 kJ/min (47–124 kJ/min).

### Glucose Metabolism

The hyperinsulinemic euglycemic clamp data indicated that pio + ex improved insulin-mediated peripheral glucose  $R_d$  more than pio (Fig. 1A). Baseline fasting glucose  $R_d$  was similar in both groups before and after intervention. Glucose  $R_d$  under hyperinsulinemic conditions (280–350 pM) was similar in both groups at week 0 ( $P = 0.37$ ), improved within each group after intervention ( $P \leq 0.0002$ ), and the improvement was greater ( $P = 0.005$ ) in the pio + ex (37%) than in the pio group (19%). Basal hepatic insulin sensitivity index was similar in both groups at week 0 ( $P = 0.21$ ) and improved within each group after intervention ( $P < 0.03$ ), and the improvement was not different between groups ( $P = 0.16$ , 25–42%; Fig. 1B). Measurement variability in the hepatic insulin sensitivity index may have limited the between-group comparison. Likewise, at baseline the ability of insulin to suppress endogenous glucose production ( $R_a$ ) was blunted in both groups. After intervention, both groups experienced equivalent significant improvements ( $P = 0.01$ , 10–15%) in this parameter (Fig. 1C).

### Body Composition

Using DEXA, baseline weight, FFM, and limb adipose mass were similar and were not significantly altered following either intervention (Table 2). Of note, limb adipose mass changes were small and not significantly different ( $P = 0.14$ ) between the pio (+298 ± 192 g, +4%) and pio + ex group (-119 ± 204 g, -2%). Total adipose mass decreased more ( $P = 0.05$ ) in pio + ex (-907 ± 586 g, -4%), and this was attributed predominantly to a decline ( $P = 0.05$ ) in trunk adipose mass (-838 ± 440 g, -6%) compared with the small changes ( $P > 0.18$ ) in total (+642 ± 468 g, +3%) and trunk adipose mass in pio (+337 ± 356 g, +2%). Abdomen  $^1\text{H-MRI}$  indicated that VAT tended to decrease more in pio + ex (-144 ± 79 cm<sup>3</sup>) than in pio (+37 ± 47 cm<sup>3</sup>,  $P = 0.06$ ), but SAT changes were small (1–3%) and not different between groups (+28 ± 74 vs. +63 ± 52 cm<sup>3</sup>,  $P = 0.70$ ; Table 2). Baseline thigh subcutaneous adipose volume was similar between groups and unchanged after both interventions (Table 2). Baseline thigh muscle volume was similar in pio and pio + ex (Table 2). After 4 mo, thigh muscle volume increased in pio + ex (5.2 ± 2.0 cm<sup>3</sup>), whereas it decreased in pio (-2.5 ± 1.2

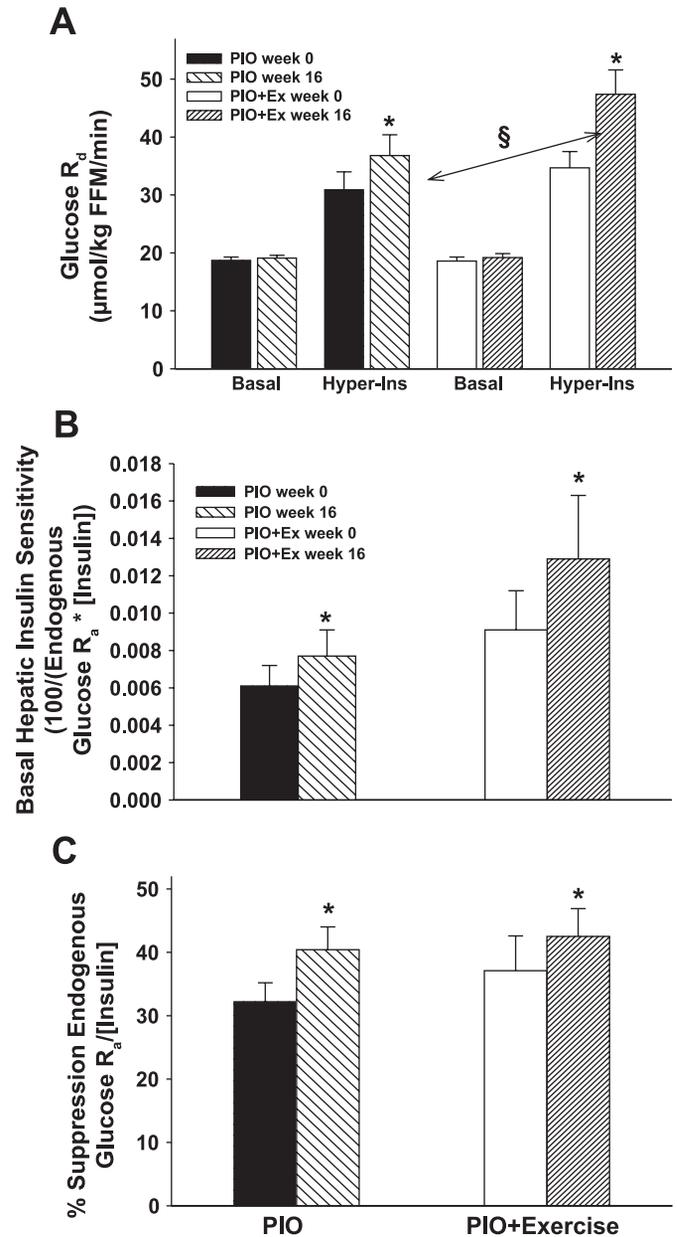


Fig. 1. Baseline and postintervention (A) basal and insulin-mediated (Hyper-Ins) peripheral glucose disposal rate (glucose  $R_d$ ; means ± SE). Basal hepatic insulin sensitivity index (B) and the ability of hyperinsulinemia (280–350 pM) to suppress endogenous glucose production rate ( $R_a$ ; C) were quantified using the hyperinsulinemic euglycemic clamp procedure with [6,6-<sup>2</sup>H<sub>2</sub>]glucose tracer infusion in HIV-infected adults ( $n = 39$ ) with baseline insulin resistance and central adiposity. A: peripheral glucose disposal was improved in both groups ( $*P \leq 0.0002$ ), but more (§ $P = 0.005$ ) in the pioglitazone plus exercise training group (pio + ex) than in the pioglitazone group (pio). B: hepatic insulin sensitivity. C: insulin's ability to suppress endogenous glucose production rate improved equivalently ( $*P < 0.03$ ) in both groups after intervention.

cm<sup>3</sup>); the between group change was different ( $P = 0.0009$ ). On average, baseline hip and lumbar spine BMD were similar between groups ( $P > 0.50$ ) and slightly lower than age-, sex-, and race-matched normal values (negative z-scores; Table 2). Hip and spine BMD and z-scores were not changed and were not differentially affected after the 4-mo interventions (Table 2).

### Liver Lipid Content

Liver  $^1\text{H-MR}$  spectroscopy at baseline indicated that average hepatic lipid content was high ( $>7\%$ ; Ref. 47) but similar ( $P = 0.12$ ) in pio ( $12.1 \pm 2.0\%$ ) and pio + ex ( $8.0 \pm 1.7\%$ ; Table 2). Overall, pio and pio + ex tended to reduce liver lipid content ( $-1.5 \pm 1.3$  vs.  $-2.6 \pm 1.4\%$ ), but the change was not different between groups ( $P = 0.60$ ).

When the groups were combined, greater reductions in total body, limb, and thigh adipose tissue content were associated with greater improvements in insulin-mediated glucose disposal (peripheral insulin sensitivity:  $r = -0.33$ ,  $P = 0.04$ ;  $r = -0.40$ ,  $P = 0.01$ ; and  $r = -0.33$ ,  $P = 0.04$ ). This was not true for changes in trunk adipose mass, VAT, liver lipid, thigh muscle volume, or adiponectin concentrations. Improvements in hepatic insulin sensitivity were not associated with greater reductions in liver lipid content ( $P = 0.12$ ,  $r = -0.26$ ).

### Fasting Lipid/Lipoprotein Concentrations

Based on National Cholesterol Education Program Adult Treatment Panel III criteria, baseline hypertriglyceridemia ( $\geq 1.7$  mM) and low HDL cholesterol concentrations ( $\leq 1.0$  mM) were noted in both groups (Table 3). Fasting triglycerides and total, LDL, and HDL cholesterol concentrations were not changed after either intervention, and no between-group differences were noted.

### Serum Adiponectin Concentration

Baseline hypo adiponectinemia ( $<10$   $\mu\text{g/ml}$ ; Refs. 2, 3, 53, and 58) was observed in both groups ( $4.7 \pm 0.8$  vs.  $4.8 \pm 0.8$   $\mu\text{g/ml}$ ; Table 3). Serum adiponectin levels increased significantly in both groups ( $+2.3 \pm 0.5$  vs.  $+1.7 \pm 0.5$   $\mu\text{g/ml}$ ,  $P < 0.002$ ; Table 3), but the increase was not different between groups ( $P = 0.41$ ). Likewise, HOMA-IR was reduced significantly in both groups ( $P < 0.004$ ; Table 3), but the magnitude of the reduction was not different between groups ( $P = 0.86$ ).

### Potential Side Effects of Pioglitazone

No serious adverse events or complications occurred. No participant developed heart failure, serious edema, or weight gain. Baseline systolic (SBP) and diastolic blood pressures (DBP) were mildly elevated (prehypertension) but similar in pio ( $133 \pm 5/84 \pm 4$  mmHg) and pio + ex ( $127 \pm 4/80 \pm 3$  mmHg). After pio, these were unchanged ( $132 \pm 4/77 \pm 2$  mmHg,  $P > 0.45$ ). After pio + ex, SBP was unchanged ( $121 \pm 4$  mmHg,  $P = 0.14$ ), but DBP declined ( $71 \pm 3$  mmHg,  $P = 0.01$ ). SBP and DBP changes were not different between the groups ( $P > 0.10$ ). Immunological and virological control was maintained during the study (Table 3). Plasma HIV RNA was undetectable ( $<100$  copies HIV RNA/ml) at baseline in all but one participant, and at 4 mo it remained undetectable in all but the same participant. Baseline CD4+ T cell counts were similar between groups and remained stable during the intervention (Table 3). Baseline hip and spine BMDs were low but not significantly worsened after pio or pio + ex (Table 2). Hepatobiliary complications were not observed; baseline transaminase and alkaline phosphatase levels were within normal limits and similar between groups and remained stable (Table 3). Hematocrit did not increase and hemoglobin levels

did not decrease in both groups, suggesting that marked fluid retention or anemia did not occur (Table 3).

### DISCUSSION

These findings indicate that 4 mo of exercise training augments the peripheral insulin-sensitizing benefits of pioglitazone in HIV-infected adults with insulin resistance and central adiposity. Insulin-mediated suppression of endogenous glucose production and an index of hepatic insulin resistance were improved equivalently in both groups, suggesting that pioglitazone mediated this improvement. These findings suggest that pioglitazone is an effective intervention for improving peripheral and central insulin sensitivity in HIV with insulin resistance and central adiposity and that exercise training provides additional beneficial effects on glucose disposal. Future studies should examine whether the added glycemic benefits of pio + ex translate into added cardiovascular benefits in HIV-infected men and women with insulin resistance and central adiposity.

Body composition changes and correlations indicated that pioglitazone did not increase (clinically or statistically) subcutaneous adipose volume in the abdomen or thigh regions; however, the current participants were not selected for the presence of peripheral lipoatrophy. Reductions in total body and limb adipose mass may be more important for enhancing peripheral insulin sensitivity than increases in adiponectin concentrations or subcutaneous adipose tissue in people living with HIV, insulin resistance, and central adiposity. The prevalence of lipoatrophy (loss of subcutaneous adipose tissue) is higher in HIV-infected adults taking cART (22–38%) than in the general population (55). HIV-lipoatrophy has been associated with peripheral insulin resistance (24, 41), can be stigmatizing, and has been associated with depressed mood and reduced quality of life (43). Efforts to reverse HIV-lipoatrophy have not been successful. Switching anti-HIV medications away from the thymidine analog nucleoside reverse transcriptase inhibitors (tNRTI) increased mean limb subcutaneous adipose mass by 150–200 g over 6 mo and 200–450 g over 12 mo (39), similar to the small change in limb adiposity noted in the current 4-mo pio group. Several studies have tested TZDs to reverse HIV-lipoatrophy in participants with and without insulin resistance (3, 8, 9, 17, 20, 21, 23, 25, 33, 34, 40, 42, 46, 48, 49, 51, 52, 57, 58). Overall, these reports indicate that rosiglitazone increased median limb fat mass by 0–250 g over 3–12 mo, and pioglitazone increased median limb fat mass  $\sim 130$  g over 12 mo in HIV-infected men and women taking tNRTI. In HIV-infected adults not taking tNRTI, rosiglitazone increased median limb fat mass 140–448 g over 3–12 mo, and pioglitazone increased median limb fat mass  $\sim 240$  g over 12 mo. Importantly, several of these reports included participants with severe lipoatrophy (limb adipose mass  $<6$  kg) and a placebo group where median limb adipose mass changes varied from  $-180$  to  $+170$  g. We found that pio + ex-induced reductions in total body and limb adipose tissue were associated with greater improvements in peripheral insulin sensitivity (glucose disposal) than the small changes in limb adipose tissue induced by pio. Limb fat changes associated with pio may have been limited by the fact that 30–40% participants were using zidovudine (tNRTI). These findings suggest that, in HIV with insulin resistance and central adiposity, exercise training-induced reductions in adipose mass add to the bene-

ficial effects of the peripheral insulin sensitizer (pioglitazone) and may reduce the incidence of DM and CVD in HIV, a group with approximately twofold greater risk for myocardial infarction and stroke than the general population (56).

Our findings confirm that combined interventions for diabetes prevention in HIV that include a lifestyle/behavioral component are more effective than a medication intervention alone (16), and these observations extend to pioglitazone plus exercise training in HIV-infected men and women with DM and CVD risk factors. The Diabetes Prevention Program (DPP) established that lifestyle intervention ( $\geq 150$  min/wk moderate-intensity physical activity aimed at reducing body weight by 7%) reduced the incidence of diabetes in high-risk adults by 58% (4.8 cases/100 person-years), whereas metformin reduced diabetes incidence by 31% (7.8 cases/100 person-years) compared with placebo (11.0 cases/100 person-years) (13, 14). In the DPP 10-yr followup, diabetes incidence was reduced 34% in those who continued lifestyle intervention and 18% in those who continued metformin. For HIV-infected adults with DM and CVD risk factors, our findings confirm the added glycemic benefits of increased physical activity (a modifiable risk factor) (31), suggest that TZD treatment alone may not optimally improve peripheral insulin sensitivity, and portend that in the long term, pio + ex may reduce diabetes risk and incidence in this vulnerable group more than pio alone.

The risk/benefit profiles for rosiglitazone and pioglitazone for the treatment of DM have stimulated a great deal of recent controversy and scrutiny (22). Pooled analyses suggest that rosiglitazone is associated with a greater risk for acute myocardial infarction than other DM medications. The FDA recently ruled to severely restrict the use of rosiglitazone for treating DM (44). Conversely, a meta-analysis of pioglitazone trials reported reduced risks for nonfatal acute MI, stroke, and all-cause mortality (30). In the current short-term study, no serious adverse events were noted with pio or pio + ex. Fasting serum lipid/lipoprotein levels were not affected by pio or pio + ex, but in past studies of HIV-infected adults, rosiglitazone was associated with proatherogenic changes in lipids/lipoproteins (8, 25, 40, 46, 51). In a 1-yr study of HIV-infected adults with severe lipodystrophy, pioglitazone increased HDL cholesterol concentrations and did not increase triglycerides or total or LDL cholesterol concentrations (49). TZDs may increase liver transaminase levels and cause edema or anemia; these were not observed in the current study and not in other studies of relatively young HIV-infected adults (8, 9, 25, 40, 49, 51). Bone demineralization is another potential TZD risk. Osteopenia/osteoporosis is prevalent in HIV-infected adults (54), and TZDs may worsen bone mineral losses. Although our study was only 4 mo in duration, we did not observe any worsening of hip or spine BMD or an increase in serum alkaline phosphatase concentrations in these participants with low baseline BMD. Longer-term studies of pioglitazone in HIV are needed.

It is not clear whether pioglitazone and exercise training act through different additive biochemical pathways in peripheral tissues. Serum adiponectin concentrations were equivalently increased after both interventions, and the prepost change in adiponectin concentration was not correlated with the improvement in insulin-mediated glucose disposal, so it does not appear that higher adiponectin concentrations (presumably by activating AMPK) mediated the greater improvement in insulin sensitivity in the pio + ex group. A similar observation was

reported in a small study of rosiglitazone for HIV-lipodystrophy; adiponectin concentration increased 107%; however, insulin-mediated suppression of endogenous glucose production and disposal were not improved (3). Serum adiponectin has pleiotropic actions, including anti-inflammatory, antiatherogenic and proinotropic (32, 53). TZDs or substantial weight loss are safe, effective strategies for increasing serum adiponectin concentrations, so these potentially beneficial actions of adiponectin need to be examined in HIV+ with hypoadiponectinemia and CVD risk.

In the current study, a reduction in visceral adiposity (VAT) only tended to be greater in the pio + ex group, and VAT change (prepost) was not correlated with the improvement in insulin-mediated glucose disposal, so it does not appear that greater reductions in visceral adiposity mediated greater improvement in insulin sensitivity in the pio + ex group. Likewise, equivalent reductions in liver lipid content were observed but were not associated with greater improvements in hepatic insulin sensitivity or insulin-mediated glucose disposal. The pioglitazone dose and duration did not significantly reduce liver lipid content, whereas rosiglitazone appears to reduce liver lipid content in HIV with lipodystrophy (not selected for insulin resistance; Refs. 51 and 52). However, rosiglitazone-induced reductions in liver lipid content were associated with undesirable increases in fasting triglycerides, an effect not observed in the current study. In HIV-lipodystrophy, rosiglitazone activated adipose tissue PPAR $\gamma$  (34, 51), but recent evidence suggests that PPAR $\gamma$  dephosphorylation may be an important mechanism for activating adipose PPAR $\gamma$  (12), and this needs to be examined in HIV-infected people treated with pioglitazone.

There were some limitations. Certain control groups (no intervention, exercise training only) were not included. A no-intervention group would rule out the potential benefits of being in a study, but it is unethical not to provide an intervention to an HIV-infected person with insulin resistance and central adiposity (discovered upon screening). And the metabolic and anthropomorphic benefits of exercise training for HIV-infected adults have been reported (31). Our focus was on whether these benefits add to the potential benefits of pioglitazone. In HIV-lipodystrophy with dyslipidemia (not selected for insulin resistance), peripheral insulin sensitivity improved 12–18% after 4 mo of resistance or aerobic exercise training (31), but only resistance training reduced total body fat. On the basis of this, we combined strength and endurance training with pioglitazone. Intracellular mechanisms by which exercise training augments the glycemic benefits of pioglitazone were not explored and should be in future studies. The small number of participants and the varied cART regimens limit our conclusions about specific anti-HIV drugs that might diminish the effects of pioglitazone and exercise training in HIV.

In summary, pioglitazone administration with increased physical activity improved peripheral insulin sensitivity more than pioglitazone alone in HIV-infected adults with insulin resistance and central adiposity. Improved insulin sensitivity was associated with exercise-induced reductions in total and limb adiposity. Pioglitazone alone did not substantially increase subcutaneous adipose content. In this 4-mo study, the safety profile for pioglitazone was favorable. The HIV-infected population is aging; their CVD morbidity and mortality are higher than the general population, so the potential anti-

inflammatory, antiatherogenic, proinotropic actions of pioglitazone and exercise training need further study in HIV-infected adults with CVD risk factors.

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#### DISCLOSURES

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