

The Impact of Exercise on the Metabolic Consequences of HIV and HAART

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Highly active antiretroviral therapy is related to side effects such as:

- a) Improvements in body composition, especially redistribution of body fat.**
- b) Hypertriglyceridemia**
- c) Glucose intolerance**
- d) Insulin resistance and diabetes mellitus**
- e) Hypertension**
- f) I do not know, I'm coming to learn.**

Regular physical exercise may contribute toward:

- a) Preventing the accumulation of abdominal fat.**
- b) Increasing lean muscle mass and improving strength.**
- c) Improving cardiovascular fitness.**
- d) Increased waist-to-hip ratio.**
- e) Improvements in systolic and diastolic blo.**
- f) I do not know, I'm coming to learn.**

Metabolic Problems in HIV

1. They are caused by the disease process itself and also by Highly Active Antiretroviral Treatment (HAART).
2. At this point, it is totally unknown what percentage of the metabolic problems is caused by the disease itself and by the HAART treatment.

Problems with HAART

The use of HAART has substantially improved survival time for those with HIV, but as a result, the long-term effects of HAART, such as:

- **Chronic disease**
- **Disability**
- **Decreased quality of life**

have to be considered in the overall approach to care.

What Characterizes Metabolic Problems?

1. Altered blood lipids (increased total and LDL cholesterol and decreased HDL cholesterol), which predisposes cardiovascular disease
2. Impaired ability to metabolize glucose and cellular insulin resistance
3. Peripheral loss of fat in the face and arms and fat deposition in the trunk and rear neck
4. Decreased bone density

What Characterizes Metabolic Problems?

5. Abnormalities and structural changes in the muscles
6. Increased inflammation (cytokine activity)
7. Failure to properly utilize, store, and excrete nutrients
8. Higher levels of oxidative stress (mitochondrial dysfunction)

1. Nolan D, Hammond E, Martin A, Taylor L, Herrmann S, McKinnon E, Metcalf C, Latham B, Mallal S. Mitochondrial DNA depletion and morphologic changes in adipocytes associated with nucleoside reverse transcriptase inhibitor therapy. *AIDS*. 2003;17:1329-1338.
2. Gelato MC. Insulin and carbohydrate dysregulation. *Clin Infect Dis*. 2003;36(suppl 2): S91-S95.
3. Carr A, Samaras K, Thorisdottir A, Kaufman GR, Chisholm DJ, Cooper DA. Diagnosis, prediction, and natural course of HIV-1 protease inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus. A cohort study. *Lancet*. 1999;353: 2093-2099.
4. Safrin S, Grunfeld C. Fat distribution and metabolic changes in patients with HIV infection. *AIDS*. 1999;13:2493-2505.
5. Grundy SM. Obesity, metabolic syndrome, and cardiovascular disease. *J Clin Endocrinol Metab*. 2004 Jun;89(6):2595-2600.

HAART-Induced Mitochondrial Myopathy.....

results in several problems, including:

1. Reductions in cytochrome-*c* oxidase
2. Inhibition of nicotinamide adenine dinucleotide (NADPH)-linked respiration and NADPH-cytochrome-*c* reductase activity
3. Decreases in mitochondrial deoxyribonucleic acid and ribonucleic acid

which ultimately lead to reduced muscle oxygen extraction-utilization in HIV+ individuals using HAART.

The Primary Metabolic Problem is...

The negative changes associated with
Cardiovascular Disease (according to morbidity
and mortality indicators)

Cardiovascular disease includes:

1. Coronary heart disease (heart attacks)
2. Cerebrovascular disease (stroke)
3. Hypertension
4. Peripheral artery disease
5. Congestive heart failure

Cardiovascular Disease

(The #1 Killer!)

1. It is the number one cause of death globally and is projected to remain the leading cause of death.
2. An estimated **17.5 million people** died from cardiovascular disease in 2005, representing **30% of all global deaths**.
3. Of these deaths, 7.6 million were due to heart attacks and 5.7 million were due to stroke.
4. Around 80% of these deaths occurred in low and middle income countries.

Preventing Cardiovascular Disease

The Adult Treatment Panel III guidelines emphasize primary prevention of cardiovascular disease and highlight the importance of **increased exercise** and **therapeutic lifestyle modification** in people with risk factors for cardiovascular disease.

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001; 285:2486-2497.

The Strategies for Management of Antiretroviral Therapy (SMART) Study Group

5,472 persons with HIV with a CD4 >350 to either continuous use of HAART (viral suppression) or episodic use of HAART (drug conservation).

Primary outcome was an opportunistic disease or death from any cause. Secondary outcome was major cardiovascular, renal, or hepatic disease.

Key Points: **SMART** Study

The drug conservation group had worse cardiovascular disease outcomes than did viral suppression group.

The drug conservation group had significantly greater risk of both fatal and non-fatal MI, stroke, coronary artery disease requiring surgery, renal disease, and liver disease per 100 years of follow-up.

The **Data** Collection on **Adverse** Events of Anti-HIV **Drugs** (**DAD**) Study Group

This is a prospective observational multi-country study of 23,437 patients infected with HIV.

The purpose of the study is to investigate the association of cumulative exposure to protease inhibitors (PIs) and nonnucleoside reverse-transcriptase inhibitors (NNRTIs) with the risk of myocardial infarction.

Key Points: Results of the **DAD** Trial Linking PI Use to MI

- 345 patients had a MI during 94,469 person-years of observation.
- The incidence of MI increased from 1.5 per 1,000 person-years in those not exposed to PIs to 6.0 per 1,000 person-years in those exposed to PIs for more than 6 years.
- After adjustment for exposure to the other drug class and established cardiovascular risk factors (excluding lipid levels), the relative rate of MI per year of PI exposure was 1.16, whereas the relative rate per year of exposure to NNRTIs was 1.05.

Key Points: Results of the **DAD** Trial

Linking PI Use to MI

- Adjustment for serum lipid levels further reduced the relative rates per year of exposure to 1.10 and 1.00, respectively.
- Most experts consider this risk to be low to moderate, depending on a patient's risk-factor burden.
- Thus, the best approach to reducing this risk even further is to address the important "modifiable lifestyle issues" of smoking, diet, and exercise.
- Increased exposure to PIs is associated with an increased risk of MI, which is partly explained by dyslipidemia, but no evidence of such an association for NNRTIs.

In the Non-HIV Population, Exercise...

Provides many benefits to health and disease, including:

1. **Cardiovascular disease**
2. **Diabetes**
3. **Metabolic Syndrome**

by resulting in a more favorable risk profile (i.e., higher levels of HDL, lower LDL and total cholesterol, and lower incidence of insulin resistance, glucose intolerance, hypertension and lower body mass index.

In the Non-HIV Population, Exercise...

These studies typically looked at exercise interventions that utilized vigorous physical activity (defined as activities of intensity greater than six metabolic equivalents (**MET**)).

A **MET** is defined by the American College of Sports Medicine as: one **MET** is equal to 3.5 ml of oxygen per kilogram (kg) of body weight per minute (1 kg = 2.2 pounds), which is equivalent to your resting metabolic rate.

What Are Corresponding MET Levels?

MET Activity

- 1 (None; sleeping or resting quietly)
- 1.5 (Light; eating, writing, driving, or showering)
- 3.5 (Moderate; level walking at 2.5 mph)
- 6 (Vigorous; walking at 5 mph or cycling 11 mph)
- 10 (Maximal; running at 6 mph)

Moderate intensity using METs decreases with age.

Exercise in the HAART Era

Cross-Sectional Evaluations of Aerobic Capacity

Effects of Exercise

Regular exercise has been found to slow down the progression of HIV and increase CD4 cell count.

One study showed that HIV patients exercising 3-4 times per week were less likely to develop AIDS than those carrying out daily exercise (1), revealing a need to slightly limit the amount of physical activity for people with HIV.

Keep in mind that the WHO's general recommendation is for one hour of moderate exercise per day for the prevention of chronic disease (2).

1. Mustafa T, Sy FS, Macera CA, Thompson SJ, Jackson KL, Selassie A, et al. (1999). Association between exercise and HIV disease progression in a cohort of homosexual men. *Ann Epidemiol*, Feb 9(2), 127-131.
2. World Health Organization. (2002). *The world health report 2002: Reducing risks, promoting healthy life*. Geneva: World Health Organization.

Cardiovascular Exercise Capacity

During a maximal exercise test on a treadmill, compared to HIV+ subjects not on HAART and HIV-controls, persons on HAART had lower:

1. Muscle oxygen extraction-utilization, which is a measure of aerobic capacity
2. Peak heart rate
3. Stroke volume at peak exercise

Cardiovascular Exercise Capacity

During testing at 3 METs, 70% of VO₂ maximum, and a maximal exercise test on a treadmill, HIV+ subjects on HAART, HIV+ subjects **NOT** on HAART, and HIV-controls were compared on oxygen consumption and the oxidative response index.

Both HIV groups performed worse than the HIV-controls and the authors concluded that the effect was **NOT** due to treatment.

Longitudinal Training Studies

Effects of Exercise Training and Metformin on Body Composition and Cardiovascular Indices in HIV-Infected Patients

Purpose of the Study:

To determine if exercise training in combination with Metformin improves cardiovascular risk indices and insulin in comparison to Metformin alone among HIV-infected patients.

Metformin has improved insulin sensitivity and cardiovascular disease risk in HIV- and HIV+ patients with visceral obesity and impaired glucose tolerance and has been suggested as a potential therapeutic strategy.

Methods:

A prospective, randomized, 3-month study of HIV patients on stable HAART with hyperinsulinemia and fat redistribution (37 subjects randomized and 25 completed).

Subjects received Metformin alone or Metformin and exercise training of 1 hour of aerobic and resistance training three times a week.

Blood pressure and endurance during sub-maximal stress testing, body composition, strength, insulin, and other biochemical parameters were determined.

Overall Results:

Compared to Metformin alone, the exercise training and Metformin group demonstrated **significant decreases** in:

1. Median waist-to-hip ratio
2. Resting systolic and diastolic blood pressures
3. Fasting insulin
4. Insulin area under the curve

and **significant increases** in:

1. Thigh muscle cross-sectional area
2. Exercise time

Lipids and resting lactate did not change significantly between treatment groups.

Strength Training Results:

	Metformin (n = 14)		Metformin and Exercise (n = 11)		P value
	Median baseline*	Median change	Median baseline*	Median change	
Leg curls	45.5 (35.5, 51.1)	2.3 (0, 8.0)	38.6 (25.0, 47.7)	18.2 (4.5, 25.0)	0.004
Leg ext	46.6 (43.9, 68.2)	1.1 (-5.1, 7.4)	40.9 (34.1, 47.7)	18.2 (4.6, 29.6)	0.010
Leg press	115.9 (100.0, 141.5)	0.9 (-6.8, 25.9)	120.0 (83.2, 138.6)	24.6 (0, 61.8)	0.094
Lat pull down	56.8 (45.5, 71.6)	-3.4 (-9.8, 4.6)	50.0 (43.2, 68.2)	18.2 (6.8, 20.5)	0.001
Arm curls	17.0 (13.1, 22.7)	-2.3 (-2.3, 0.3)	13.6 (10.0, 18.2)	4.6 (2.3, 6.8)	0.001
Chest press	70.5 (44.3, 88.1)	1.1 (-2.8, 5.7)	63.6 (50.0, 86.4)	13.6 (5.0, 20.5)	0.024
Lactic acid	1.6 (1.2, 2.0)	0.4 (0.1, 0.7)	1.7 (1.5, 1.9)	0.2 (-0.1, 0.6)	0.493

Exercise numbers are in kilograms and the p value is for the comparison of median change from baseline between treatment groups using the Wilcoxon's rank-sum test.

Conclusions:

This study suggests that exercise training in combination with Metformin significantly improves cardiovascular and biochemical parameters more than Metformin alone in HIV-infected patients with fat redistribution and hyperinsulinemia.

Strength was also significantly increased in the combination group without a change in resting lactate levels, suggesting that vigorous exercise can be used in HIV+ patients receiving Metformin without a predisposing risk of lactic acidosis.

The treatment also proved to be safe, well-tolerated, and may be a useful strategy to decrease cardiovascular risk among persons living with HIV.

**Effects of a Lifestyle Modification
Program in HIV-Infected Patients
with the Metabolic Syndrome**

Purpose of the Study:

To determine if lifestyle modification improves waist circumference, blood pressure, fasting blood sugar, triglycerides, and HDL-cholesterol (metabolic syndrome criteria variables) among HIV-infected patients with the metabolic syndrome.

Methods:

Subjects were randomly assigned to an intensive lifestyle modification program, which included weekly one-on-one counseling sessions with a registered dietician, or observation (control group) for 6 months (34 patients were randomized and 28 completed).

Blood pressure, body composition, sub maximal stress testing, lipids, and other biochemical parameters were compared between the two groups.

Lifestyle Modification Intervention:

Participant goals were:

1. Healthy Eating

- a. $\leq 35\%$ of total calories from fat
- b. $< 7\%$ of total calories from saturated fat
- c. up to 10% of total calories from polyunsaturated fat with emphasis omega 3 fatty acids
- d. less trans fatty acids
- e. up to 20% of total calories from monounsaturated fat
- f. 25 to 35 g of soluble and insoluble fiber per day

Lifestyle Modification Intervention:

Participant goals were:

2. Physical Activity

- a. 3 hours per week at moderate intensity
- b. Greater than or equal to 10,000 steps in daily activity measured by pedometer
- c. Self-monitoring

Schedule of Lifestyle Modification Program Sessions:

Session	Topic	Initial session	Reinforcement
1	Welcome	Week 1	Weeks 2, 19
2	Being active: move those muscles	Week 2	Weeks 3, 19
3	Being a savvy fat detective	Weeks 3-5	Weeks 6, 20
4	Healthy eating with a fiber focus	Weeks 6-8	Weeks 9, 20
5	Being active	Week 9	Weeks 10, 21
6	Taking charge of what's around you	Week 10	Weeks 11, 21
7	Four keys to healthy eating out	Weeks 11-12	Weeks 13, 22
8	Jump start your activity plan	Week 13	Weeks 14, 22
9	Slippery slope of lifestyle change	Weeks 14-15	Weeks 16, 23
10	Problem solving and social cues	Week 16	Weeks 17, 23
11	You can manage stress	Week 17	Weeks 18, 24
12	Ways to stay motivated	Week 18	Weeks 19, 24

Overall Results:

Compared with the control group, the lifestyle modification group demonstrated **significant decreases** in:

1. Waist circumference
2. Systolic blood pressure
3. Hemaglobin A1C
4. Lipodystrophy score
5. Increased activity in METs

Lipid levels did not improve.

Activity, Fitness, and Lipodystrophy Results:

	Lifestyle Modification		Control Group		P value	
	Baseline (n = 16)	Change at 6 months (n = 12)	Baseline (n = 18)	Change at 6 months (n = 16)		
MAQ (MET-hours/week)		33.2 ± 12.1	17.7 ± 14.3	61.3 ± 17.3	33.1 ± 12.7	0.014
VO2max (ml/kg/minute)		19.8 ± 1.6	0.2 ± 1.2	19.7 ± 1.5	-2.0 ± 0.7	0.110
Lipodystrophy score		3.9 ± 0.4	1.2 ± 0.3	4.1 ± 0.3	0.9 ± 0.6	0.006

Modifiable Activity Questionnaire (MAQ) physical activity level was calculated as the product of the duration and frequency of each activity (in hours per week), weighted by an estimate of the MET of that activity and summed for all activities performed, with the result expressed as the average MET-hours per week.

VO2max (ml/kg/minute) for the measurement of cardiorespiratory fitness during cycle ergometry.

Lipodystrophy scores were calculated based on an evaluation of face, neck/shoulders, arms, abdomen, and hips/legs with graded values between 0 and 2 for fat loss or accumulation.

P value is for change the between treatment groups at 6 months.

Conclusion:

Intensive lifestyle modification significantly improved important cardiovascular risk indices in HIV+ patients with metabolic syndrome.

Lifestyle modification may be a useful strategy to decrease cardiovascular risk in this population.

**Effects of a Supervised Home-Based
Aerobic and Progressive Resistance
Training Regimen in Women Infected
With Human Immunodeficiency
Virus**

Purpose of the Study:

To determine the effects of a home-based exercise program on fat distribution and metabolic abnormalities in women infected with HIV.

Methods:

A 16-week randomized intervention of a supervised home-based progressive resistance training and aerobic exercise program in 40 HIV-infected women with increased waist-hip ratio and self-reported fat redistribution.

Cardiorespiratory fitness was determined by calculated maximum oxygen consumption (VO_2max) and strength by 1-repetition maximum.

Cross-sectional muscle area and muscle attenuation were measured by computed tomography.

Results:

Subjects randomized to exercise had **significant improvement** in:

1. VO2max
2. Endurance
3. Strength at the knee extensors, pectoralis, knee flexors, shoulder abductors, ankle plantar flexors, and elbow flexors
4. Total muscle area and attenuation

No significant difference was seen in lipid levels, blood pressure, or abdominal visceral fat between the groups, but subjects randomized to exercise reported improved energy and appearance.

Fitness and Strength Results:

	Exercise Group (Mean ± SEM)		Control Group (Mean ± SEM)		P Value
	Baseline (n = 20)	Change at 16 wk (n = 19)	Baseline (n = 20)	Change at 16 wk (n = 19)	
Fitness measures					
VO2max (mL/kg/min)	16.9 ± 1.0	1.5 ± 0.8	15.3 ± 1.1	-2.5 ± 1.6	<.001
Submax bike exercise (min)	6.1 ± 0.4	1.0 ± 0.3	5.0 ± 0.3	-0.6 ± 0.3	<.001
6-min walk (m)	489 ± 20	34 ± 11	474 ± 14	-6 ± 15	.009
Strength measures (kg)					
Knee extensors	22.1 ± 1.8	33.2 ± 4.4	29.5 ± 3.5	0.8 ± 1.5	<.001
Pectoralis	19.1 ± 1.0	13.9 ± 1.2	18.0 ± 1.2	0.4 ± 0.7	<.001
Knee flexors	9.6 ± 1.2	8.4 ± 1.0	6.0 ± 1.0	-0.3 ± 0.5	<.001
Shoulder abductors	3.7 ± 0.2	2.4 ± 0.3	3.3 ± 0.3	0.3 ± 0.1	<.001
Ankle plantar flexors	22.4 ± 2.4	31.5 ± 4.0	22.8 ± 2.2	1.9 ± 1.2	<.001
Elbow flexors, right arm	6.0 ± 0.2	3.5 ± 0.6	5.8 ± 0.5	0.5 ± 0.4	<.001
Elbow flexors, left arm	5.9 ± 0.2	3.6 ± 0.6	5.2 ± 0.4	0.9 ± 0.3	<.001

P value is for change the between treatment groups at 16 weeks.

Conclusions:

This home-based exercise regimen improved measures of physical fitness in HIV+ women. The effects on strength were most significant, but improvements in cardiorespiratory fitness, endurance, and body composition were also seen.

Dolan, SE. et al. Effects of a Supervised Home-Based Aerobic and Progressive Resistance Training Regimen in Women Infected With Human Immunodeficiency Virus. Arch Intern Med. 2006; 166: 1225-1231.

Summary of Benefits

These studies indicate that moderate levels of physical activity are safe and beneficial in the short-term for individuals infected with HIV.

Questions remain regarding the results of exercise regimens and physical activity structured over years after a positive diagnosis of HIV.

Progressive resistance training should be particularly important, in light of wasting still being a problem for persons with HIV.



Exercise and HAART

Despite our limited knowledge about the specific benefits of exercise in HIV+ patients on HAART, physical activity is recommended for the treatment and prevention of cardiovascular disease, lipodystrophy, insulin resistance, and health related quality of life.

Aberg, J.A. (2003). Cardiovascular risk among HIV-positive patients on antiretroviral therapy. *Journal of International Association of Physicians in AIDS Care (Chic. Ill.)* . 2(Suppl 2), S24-S39.

Bergersen, B.M., Sandvik, L., Bruun, J.N., & Tonstad, S. (2004). Elevated Framingham risk score in HIV-positive patients on highly active antiretroviral therapy: Results from a Norwegian study of 721 subjects. *European Journal of Clinical Microbiology & Infectious Diseases*, 23, 625-630.

Clingerman, E. (2004). Physical activity, social support and health-related quality of life among persons with HIV disease. *Journal of Community Health Nursing* , 21, 179-197.

Cardiovascular Disease Risk: Key Points to Share with Patients

- As HIV infection becomes a chronic condition, it is important to address other health issues, such as cardiovascular risk.
- Some HAART agents are thought to increase the risk of cardiovascular disease, so changing the regimen might reduce risk.
- Some studies suggest that treatment interruption actually increases the risk of cardiovascular disease.
- Research to better understand the association of HAART and cardiovascular disease is still ongoing.
- Although long-term heart disease risks are a concern, control of HIV infection is still the primary objective.

Exercise Recommendations

The person's frequency and intensity of exercise will have an impact on the level of wasting, alterations in body fat deposition, and other long-term complications of HIV disease and HAART.

When recommending exercise, limitations should be considered, including barriers such as peripheral neuropathy, pain, and fatigue.

Exercise Recommendations

Taking into consideration any limitations, persons living with HIV/AIDS should engage in at least 3.5 hours of physical activity per week, ideally spread over 3-5 days.

1. Activities that are *liked* should be picked to increase adherence.
2. Exercising all muscles is very important.
3. Choose moderate kinds of activity, like brisk walking.
4. Work up to the goals *slowly* without experience in a regular exercise program.

Exercise Recommendations



Four Primary Components of Designing an Exercise Program:

1. **Frequency:** How many days per week?
2. **Intensity:** What percentage of maximal heart rate?
3. **Duration:** How long in a given bout?
4. **Mode:** What type of exercise?

Some Areas of Needed Research

Further research on endothelial cell function and vascular preservation in response to physical activity.

The role of weight training activities on bone mineral density and body composition because of the negative consequences of HIV and HAART.

Specific exercise guidelines for those with HIV disease are lacking, which are readily important for promoting cardiovascular and autonomic health.

A dose-response relationship of exercise training and HIV disease pathologies is needed.

Some Areas of Needed Research

Natural killer cell number and function in HIV in response to physical activity still remains unknown.

The mechanistic effects of aerobic fitness on vascular and autonomic function in HIV are not known.

Assessment of arterial compliance and autonomic modulation in response to varying intensities of exercise is also important to modulate autonomic dysfunction and its resultant effect on cardiac and vascular pathology.

Thank you for your attention!

Highly active antiretroviral therapy is related to side effects such as:

- a) Improvements in body composition, especially redistribution of body fat.**
- b) Hypertriglyceridemia**
- c) Glucose intolerance**
- d) Insulin resistance and diabetes mellitus**
- e) Hypertension**
- f) I'm sorry, I did not learn.**

Regular physical exercise may contribute toward:

- a) Preventing the accumulation of abdominal fat.**
- b) Increasing lean muscle mass and improving strength.**
- c) Improving cardiovascular fitness.**
- d) Increased waist-to-hip ratio.**
- e) Improvements in systolic and diastolic blo.**
- f) I'm sorry, I did not learn.**