Cardiovascular/Aerobic Training and the Impact on Cardiovascular Conditioning and Mitochondrial Functioning on HIV

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Cardiovascular Manifestations of HIV Infection in HAART Era

1. Dilated cardiomyopathy (10-30% prevalence)
2. Infective endocarditis (6-34% prevalence)
3. Pericardial effusion (5-46% prevalence, but is thought to be declining with HAART)
4. Pulmonary arterial hypertension (1 of 200 HIV patients)
5. Coronary artery disease (Increasing with HAART)
6. Myocardial infarction (4 x more prevalent with PIs)
7. Cardiovascular disease (Increasing with HAART)
Cardiovascular Manifestations of HIV Infection in HAART Era

8. Lower HDL cholesterol
9. Higher triglycerides
10. Higher total cholesterol
11. Increased visceral adiposity
12. Increased LDL cholesterol

The etiology of cardiovascular manifestations in HIV-infected patients is likely multifactorial, with recent studies suggesting a complex interaction between HAART, HIV itself, immunological, virological, and conventional factors.
Problems with HAART, especially Protease Inhibitors

At this point, it is still unknown and controversial what percentage of the cardiovascular manifestations is attributed to HIV itself and to HAART. It is likely multifactorial or duplicative.
results in:

1. Treatment-naive HIV-infected subjects demonstrate mtDNA depletion in peripheral blood mononuclear cells

2. mtDNA level was not only positively correlated with CD4+ T-cell count, but inversely correlated with plasma viral loads

HAART-Induced Mitochondrial Myopathy....

results in several problems, including:

1. Reductions in cytochrome-c oxidase
2. Inhibition of nictotinamide 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.

HAART-Induced Mitochondrial Dysfunction

NRTIs inhibit mitochondrial DNA polymerase γ, which is the only polymerase used in mitochondrial DNA replication, and inhibit its synthesis, resulting in reduced cellular energy production.

Inhibition of DNA polymerase γ and other mitochondrial enzymes can gradually lead to mitochondrial dysfunction and cellular toxicity.

The clinical manifestations of NRTI-induced mitochondrial toxicity resemble those of inherited mitochondrial diseases (i.e., lactic acidosis, myopathy, nephrotoxicity, peripheral neuropathy, and pancreatitis).

The morphologic and metabolic complications of this syndrome are similar to those of the mitochondrial disorder known as multiple symmetric lipomatosis, suggesting that this too may be related to mitochondrial toxicity.

AZT causes an increase in the urinary excretion of 8-oxo-dG (a marker of oxidative damage to DNA).

AZT also causes oxidation of mitochondrial DNA, mitochondrial glutathione, and lipids (measured as malondialdehyde).

This oxidative damage may be due to an increased peroxide production by muscle mitochondria.

In Light of the Cardiovascular Problems, What Can Be Done?

1. Altering HAART regimens to determine those that are most efficacious for the immune system, while lessening the negative impact on the cardiovascular system; requires extensive clinical study.

2. Improving dietary habits to reduce saturated and trans fat intake, refined and processed sugar, and animal proteins

3. Cardiovascular/Aerobic exercise
In the Non-HIV Population, Cardiovascular Exercise...

Provides many benefits to the spectrum of diseases associated with:

- coronary artery and cardiovascular disease and the co-morbid conditions of diabetes and 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 fat and body mass index)

In Type 2 Diabetes, Cardiovascular Exercise...

Resulted in weight loss, improved VO2max and insulin sensitivity, increases in skeletal muscle mitochondrial density, cardiolipin content, and mitochondrial oxidation enzymes. Improvement in mitochondrial content strongly correlated with intervention-induced improvement in HbA1C and fasting plasma glucose.

Thus, a 4-month intervention can restore mitochondrial content and functional capacity in skeletal muscle in type 2 diabetic patients. The improvement in the oxidative capacity of skeletal muscle may mediate hyperglycemia and insulin resistance.

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

1. Peak heart rate

2. Arteriovenous oxygen difference

whereas peak stroke volume was higher and peak cardiac output was not different

Exercise Training in HIV-1-Infected Individuals with Dyslipidemia and Lipodystrophy

Purpose of the Study:

This study tested the hypothesis that aerobic exercise training added to a low-lipid diet may have favorable effects in HIV-infected individuals with dyslipidemia and lipodystrophy.
Methods:

Thirty HIV+ subjects with dyslipidemia and lipodystrophy, all of whom were using PIs and/or NNRTIs, were randomly assigned to participate in either a 12-wk program of aerobic exercise or a 12-wk stretching and relaxation program. All subjects received recommendations for a low-lipid diet.

Baseline and follow-up peak oxygen uptake, body composition, CD4, viral load, lipid profile, and plasma endothelin-1 levels were measured.
Exercise Intervention:

The aerobic exercise program consisted of 36 sessions of 1 hour each, performed three times per week. Each session included a 15-min stretching warm-up period, followed by 30 min of aerobic exercise at the target intensity, and ended with 15 min of stretching exercises to cool down. The aerobic exercise part of each session was continuous. The exercise group ran at a speed that resulted in a Heart Rate of 70-85% of the HRmax obtained in the maximal exercise test.

Maximal oxygen consumption was conducted at baseline and follow-up on a treadmill with an initial speed of 3 km/hour and a 2% incline with continuous increments in speed and incline to reach volitional fatigue in approximately 10 min.
Overall Results:

Peak oxygen uptake increased significantly in the Diet and Exercise group (mean ± SD)

- **baseline**: 32 ± 5 mL/kg/min
- **follow-up**: 40 ± 8 mL/kg/min

but not in the Diet Only group

- **baseline**: 34 ± 7 mL/kg/min
- **follow-up**: 35 ± 8 mL/kg/min

Body weight, body fat, and waist-to-hip ratio decreased significantly and similarly in the two groups.

Changes did not occur in immunologic variables, triglycerides, total cholesterol, HDL cholesterol, or endothelin-1 levels.
Conclusions:

HIV-positive individuals with lipodystrophy and dyslipidemia participating in a short-term intervention of low-lipid diet and aerobic exercise training are able to increase their functional capacity without any consistent changes in plasma lipid levels.
The Effect of Exercise Training on Aerobic Fitness, Immune Indices, and Quality of Life in HIV+ Patients

Purpose of the Study:

To determine whether cardiovascular exercise improves aerobic fitness, immune indices, and quality of life.
Methods:

Thirty-four HIV+ subjects participated in a 6-week aerobic exercise training program. Subjects were assigned to three groups: control (no regular aerobic exercise), moderate exercise, and heavy exercise training. At study entry and exit, aerobic function, CD4 counts, HIV RNA measurements, and quality of life were evaluated.
Exercise Intervention:

Subjects were randomized to: (1) control group was advised to maintain their current level of activity without changes; (2) moderate intensity exercise training group performed 1 hour of exercise three times per week for 6 weeks at 80% of the lactic acidosis threshold (LAT) work rate (determined from the entrance cardiopulmonary exercise test); (3) heavy intensity exercise training group performed exercise three times per week for 6 weeks at a work rate equal to 50% of the difference between their LAT and their VO2max. This group performed a proportionally shorter amount of exercise while maintaining the total work per session identical to the moderate group. In this study, this resulted in training times of approximately 30-40 min. All exercise training sessions were performed on a calibrated cycle ergometer.
Exercise Testing:

Each subject performed a cardiopulmonary exercise test with gas exchange measurements at study entry and after 6 weeks of participation to accurately determine aerobic function as measured by the gas exchange LAT and VO2max.

LAT was defined as the VO2 above which the VCO2 output increased more rapidly than the VO2. This was determined from a plot of VCO2 as a function of VO2. Peak VO2 was defined as the maximally tolerated VO2.
Overall Results:

Aerobic fitness increased significantly in both exercise groups relative to the control group.

After 6 weeks of exercise training, LAT and VO2max changes (%, pre to post) in the three groups were (mean ± SE):

Control:  -4% ± 6 and -7% ± 5
Moderate:  10% ± 9 and -2% ± 4
Heavy:  23% ± 8 and 13% ± 4

Immune indices changed very little among all three groups. Lipid levels did not improve. Quality of life markers improved in both exercising groups but not the control group.
Conclusion:

Exercise training resulted in a substantial improvement in aerobic function, while immune indices and lipids were essentially unchanged. Quality of life markers improved significantly with exercise.
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 (VO2max) 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:

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

*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.

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.


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!