Effectiveness of a Group-Based Aerobic Exercise Intervention in HIV+ Patients: A Pilot Study

A DISSERTATION SUBMITTED TO THE GRADUATE DIVISION OF THE UNIVERSITY OF HAWAIʻI AT MĀNOA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

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ABSTRACT

Background: Exercise is recommended for HIV+ patients to control their disease as well as HAART side effects. Unfortunately, only 25 to 28.2% of HIV+ individuals engage in moderate physical activity and drop-out rates range from 45 to 87% in HIV+ cohorts. Group exercise has been shown to improve compliance. Therefore, the purpose of this study was to evaluate the effectiveness of a group-based aerobic exercise program in HIV+ individuals.

Methods: A pretest-posttest design was used to evaluate the effects of a 12 wk group-based aerobic exercise program on fitness level, lipid levels, insulin sensitivity, body composition, and quality of life in HIV+ individuals. Participants were 18 sedentary HIV+ males between 32 and 59 years of age (mean 45 ± 6.34) on HAART.

Results: Eighteen participants were enrolled; nine completed the exercise program and six of the nine were considered compliant, attending >70% of the exercise sessions. Improvements (P=0.03) in triglyceride level and health transition scores (quality of life dimension) (P=0.02) were seen post intervention. Improvements in VO$_{2\text{max}}$ (P = 0.03) were revealed among the six compliant participants. Self-efficacy for exercise and group cohesion were measured pre and post intervention, and provided descriptive information. Self-efficacy scores were lower for those who withdrew (53.66± 3.49) compared to those who completed the exercise intervention (64.22±17). Participants who were compliant (52.33±6.10) demonstrated more cohesiveness than those who were not (71.34 ±9.4).

Conclusion: Those who completed the program displayed lower triglyceride levels and felt better about their overall physical health and emotional condition at the conclusion of
the exercise program. Participants who withdrew were less confident that they could
overcome barriers to exercise than those who completed the study. Not surprisingly,
compliant participants felt more united as a group. Within the limitations of this study, a
12 wk group-based aerobic exercise program resulted in improvements in
cardiorespiratory fitness. Additionally, no negative effects on immune function in
HAART treated HIV+ individuals were found further supporting group-based aerobic
exercise programs are a viable adjunct treatment option.
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Part I
INTRODUCTION

Highly Active Antiretroviral Therapy (HAART) minimizes Human Immunodeficiency Virus (HIV) replication and improves immune function, which has reduced mortality rates and extended life expectancy [1]. Though HAART significantly enhances the management and clinical outcome of HIV with increased survival rates, these favorable effects are limited by the development of metabolic disorders including dyslipidemia, increased central adiposity, and insulin resistance [2, 3]. Metabolic syndrome is a combination of the aforementioned disorders and results in a potential increased risk for cardiovascular disease and diabetes [4, 5]. Even after adjustment for age, sex, cholesterol level, physical activity, and smoking, metabolic syndrome was found to double coronary heart disease mortality in HIV+ individuals [3] and has been associated with a five to eight fold increased diabetes prevalence [4].

Exercise training and physical activity are well-known to have positive effects on risk factors associated with metabolic syndrome including central adiposity, very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), triglycerides, and high-density lipoproteins (HDL) in people who are HIV-negative [6, 7]. Exercise improves cardiorespiratory fitness in HIV+ individuals [8-11], however, results are variable regarding hypertension, hyperlipidemia, diabetes mellitus, and visceral fat mass [8-13]. Despite this variation, exercise has proved to have a positive effect on metabolic
parameters in HIV+ patients [9, 14]. Therefore, exercise prescription is a viable alternative to additional drug therapy [13].

Regular exercise is recommended for HIV+ patients to control their disease as well as pharmacological side effects [15]. Despite this recommendation, only 25 [16] to 28.2% of HIV+ individuals engage in moderate physical activity according to Healthy People 2010 guidelines [17]. Even after initiation of an exercise program, drop-out rates are problematic ranging from 45 to 87% in HIV+ cohorts [10, 12, 18-20]. The majority of adult participants prefer to exercise with others rather than alone, [21-23] as group exercise adds psychological and social support [19]. Consequently, compliance in group-based programs exceeds individually based programs [19, 20].

Therefore, the purpose of this study was to evaluate the effects of a group-based aerobic exercise program on fitness level, lipid levels, insulin sensitivity, body composition, and quality of life (MOS-HIV) in HIV+ individuals.
METHOD

Research Design

A pretest-posttest design was used to evaluate the effectiveness of a 12 wk group-based aerobic exercise program for HIV+ individuals. The independent variable was test (pre, post) and dependent variables included: fitness level, lipid levels, insulin sensitivity, body composition, and quality of life (MOS-HIV).

Participants

Participants were 18 HIV+ males between 32 and 59 years of age (mean 45 ± 6.34). Inclusionary criteria consisted of: a stable HAART regimen defined as no change in medications six months prior to the study; and no regular aerobic conditioning in the previous three months. Regular aerobic conditioning was defined as performing more than 30 minutes of an aerobic activity at an intensity of five metabolic equivalents [24] and more than two days per week. Exclusionary criteria consisted of: Acquired Immune Deficiency (AIDs); neurological defects (i.e. dementia, neurological disease, multiple sclerosis, brain tumor, and Parkinson’s disease); absolute contraindications to exercise as outlined by the American College of Sports Medicine [25] (APPENDIX B); or any condition in the opinion of the investigators that would interfere with the study.

Informed consent forms, (APPENDIX A) approved by the University Institutional Review Board, Human Studies Program were signed by all participants prior to the study.
Clinical Research Protocol

All tests were conducted in a clinical laboratory. Main outcome measures were assessed at entry and 12 wks. The Physical Activity Readiness Questionnaire (APPENDIX D) and Self-Efficacy for Exercise Scale [26] (APPENDIX H) were completed only at the entry visit. Entry and 12 wk visits also included: Medical Outcomes Study HIV Health Survey (MOS-HIV) [27] (APPENDIX J); drug test; 12 hour fasting blood draw; dualenergy x-ray absorptiometry scan (Lunar Prodigy, version 8.8, GE Medical Systems, Madison, WI); and graded maximal exercise tests. Participants completed two additional questionnaires only at the 12 wk visit: the Physical Activity Group Environment Questionnaire (PAGEQ) [28] (APPENDIX K) and exercise instructor evaluation (APPENDIX L).

Medical Outcomes Study HIV Health Survey (MOS-HIV)

The MOS-HIV is a brief, comprehensive measure of health-related quality of life used widely in HIV. The 35-item questionnaire takes approximately five minutes to complete and includes the following dimensions: health perceptions, pain, physical, role, social and cognitive functioning, mental health, energy, health distress, quality of life, and health transition. Each dimension was scored on a zero-100 scale (higher scores indicated better health). The MOS-HIV has proved to be internally consistent, correlate with concurrent measures of health, discriminate between distinct groups, predict future outcomes and responsive to changes over time.[29]
**Self-Efficacy for Exercise Scale (SEE)**

The Self-Efficacy for Exercise Scale (SEE) is a nine-item questionnaire that takes approximately two to five minutes to complete. Participants provided responses ranging from zero to nine, (higher scores indicated higher levels of self-efficacy, maximum score of 81).[30]

**Physical Activity Group Environment Questionnaire (PAGEQ)**

The Physical Activity Group Environment Questionnaire (PAGEQ) is a 21-item instrument that takes approximately five minutes to complete and assesses social and task cohesion in both individual and group dimensions. Subscales measure the degree to which the respondent is attracted to and feels the group is united around it’s social and task activities. Participants provided responses ranging from one to four, (lower scores indicate higher levels of cohesion). [28]

**Maximal Graded Exercise Test**

Maximal oxygen consumption (VO$_2$$_{\text{max}}$) data collection began with a five minute warm up on a cycle ergometer (Model 818 E, Monark, Stockholm, Sweden) at a self-selected pace. The VO$_2$$_{\text{max}}$ graded cycling protocol began at a workload (60 rpm) of 50 Watts (W) and was increased by 12.5W every minute.[31]. A Max IIa metabolic cart (AEI technologies, Naperville, IL), via standard open circuit spirometry techniques, was used to collect respiratory exchange ratio, volume of oxygen consumed per minute (VO$_2$), and volume of carbon dioxide produced per minute (VCO$_2$). Calibration was performed prior to each test and was monitored to ensure that the values had remained
stable. Electrocardiogram (ECG) output, blood pressure, heart rate, and perceived exertion and local muscular fatigue, determined from the Borg ratings of perceived exertion (RPE) scale [32] (APPENDIX M), were assessed and documented every two minutes throughout testing. Heart rate was monitored via a Polar sensor display (Polar Electro, Lake Success, NY), compatible with the built-in interface. Exercise testing was administered by certified athletic trainers with a physician present. The American College of Sports Medicine’s guidelines for termination of exercise testing were strictly followed [25] (APPENDIX C). Verbal encouragement was given throughout the tests until volitional exhaustion. The exercise tests were considered maximal if one of the following criteria were met: a plateau in heart rate (HR); a plateau in oxygen uptake with increased workload; respiratory exchange ratio (RER) > 1.15; a venous lactic acid concentration of > 8 mmol; and RPE > 17 [33]. Cool-down was completed at a self-selected pace after the tests. Blood lactate samples were collected pre- and seven minutes post-exercise from a free flowing digit puncture and analyzed via a Lactate Plus Lactate Meter (Nova Biomedical Co., Waltham, MA).

**Training Protocol**

The aerobic training protocol was performed at a public park three times per week for 12 weeks in groups of two to 10 participants. Each exercise session consisted of: a standardized 10 minute warm-up; continuous aerobic exercise for 20-40 minutes; and concluded with five minutes of static stretching. Aerobic exercise intensities ranged from 50 – 80% of heart rate reserve (HRR). Initial fitness levels defined work level (walk, jog, or run) to obtain the appropriate intensity. Heart rate reserve was calculated as maximal
heart rate (HR_{max}) – resting heart rate (HR_{rest})[34]. Resting heart rate was assessed in a seated position during a five minute period with continuous monitoring of HR by electrocardiogram (Q-Stress, Cardiac Science, Bothell, WA) with the lowest HR value recorded as HR_{rest}.[35, 36] Target HR for a given exercise intensity was calculated as follows: ((\text{fraction of target intensity} \times \text{HRR}) + \text{HR}_{\text{rest}}) [34]. Heart rate was continuously monitored to ensure maintenance of individual exercise prescription.(Heart Rate Watch; Polar, Kempele, Finland) Initial intensities were prescribed based on the talk test and comfort level that caused a sensation of increased breathing, but still allowed for comfortable speaking in complete sentences.[37] The exercise intensity just below the point where they could no longer speak comfortably served as the starting point for each individual’s exercise program. Investigators increased exercise intensity in increments of five % HRR and duration in increments of two minutes over the course of 12 weeks. Duration and intensity were never increased during the same exercise session nor did they exceed 80% HRR or 40 minutes. All sessions were led and supervised by two certified athletic trainers.

**Statistical Analysis**

Data were analyzed using Statistical Analysis Software (SAS) Version 9.1 English Software package (SAS Institute Inc., Cary, North Carolina, USA). Treatment effects over time were compared by paired t-tests. The primary analysis was conducted utilizing only complete data. The significance level was set at \( p \leq 0.05. \)
RESULTS

Eighteen participants were enrolled and nine (completers) completed the exercise program. Nine individuals (non-completers) dropped out of the study due to discontinuing antiretroviral medications (1) illness (2), injury (2), inconvenience (1), family issues (1) and depression (2). Table 1 presents the demographic, physical, clinical characteristics, self-efficacy, and quality of life parameters for completers and non-completers at entry. Non-completers had significantly lower VO$_{2\text{max}}$ values than completers ($P=0.04$) at entry. Although not significant, completers had higher self-efficacy scores at entry ($P=0.08$). Six of the nine completers were considered compliant, attending 70% or more of the exercise sessions. Three completers fell below this mark attending 36%, 55% and 58% of exercise sessions. Table 2 presents exercise prescription data for all completers. On average completers exercised for 27.58 ± 1.92 minutes at 68% ± .09 HRR.

No significant differences in VO$_{2\text{max}}$ values were revealed from pre to post intervention among completers; however, there was a significant improvement in VO$_{2\text{max}}$ ($P = 0.03$) among those who were compliant (>70% attendance, n=6). Mean values of this sub-group of completers were 29.52 ± 4.86 (mL/kg$^{-1}$/min$^{-1}$) at entry and 34.18 ± 8.12(mL/kg$^{-1}$/min$^{-1}$) at 12 wks, an average increase of 15%. Triglyceride levels were lower ($P=0.03$) and health transition scores were higher ($P=0.02$) post intervention as compared to entry in completers. No significant differences were revealed for any other dependent variables. All means, standard deviations and statistic results for demographic, physical and clinical characteristics for completers at entry and 12 wks are presented in Table 3. All means, standard deviations and statistic results for quality of
life (MOS-HIV) for completers at entry and 12 wks are presented in Table 4. Physical Activity Group Environment Questionnaire data at 12 wks for completers are presented in Table 5.

| Table 1. Demographic, Physical, Clinical Characteristics, Quality of Life (MOS-HIV), and Self-Efficacy for Completers and Non-Completers at Entry (n=18) |
|-----------------|-----------------|-----------------|
| Variable                | Completers (n=9) | Non-completers (n=9) |
| Age (years)            | 43.00 ± 6.76     | 47.33 ± 5.48     |
| Race                     |                  |                  |
| Caucasian                | 5                | 5                |
| Hispanic                 | 1                | 0                |
| Pacific Islander         | 2                | 3                |
| Indian                   | 1                | 0                |
| African American         | 0                | 1                |
| Duration of HIV infection (years) | 14.44 ± 9.53 | 9.00 ± 5.15 |
| CD4+ cell number (cells/mm³) | 520.22 ± 215.92 | 492.11 ± 254.02 |
| Viral Load               |                  |                  |
| Undetectable            | 7                | 7                |
| Detectable               | 2                | 2                |
| Body weight (kg)         | 76.52 ± 13.82    | 82.42 ± 13.50    |
| Body fat (%)             | 27.46 ± 6.14     | 32.67 ± 8.43     |
| *VO₂max (mL/kg·1/min·1) | 33.71 ± 10.30    | 27.01 ± 4.24     |
| Triglycerides (mg.dL-1)  | 122.67 ± 50.83   | 198.89 ± 130.56  |
| Total cholesterol (mg.dL-1) | 174.33 ± 19.78 | 180.56 ± 30.94 |
| HDL cholesterol (mg.dL-1) | 55.56 ± 15.53   | 47.78 ± 16.81    |
| LDL cholesterol (mg.dL-1) | 95.22 ± 25.84   | 92.75 ± 16.59    |
| Non-HDL cholesterol (mg.dL-1) | 118.78 ± 30.12 | 132.78 ± 29.45  |
| Insulin (mg.dL-1)        | 11.21 ± 10.52    | 10.63 ± 8.37     |
| Glucose (mg.dL-1)        | 93.33 ± 17.10    | 85.67 ± 11.65    |
| Insulin Sensitivity (%)ᵃ | 99.64 ± 61.76    | 100.29 ± 64.17   |
| MOS-HIV                  |                  |                  |
| Quality of Life          | 75.00 ± 17.67    | 63.89 ± 13.17    |
| General Health Perception| 66.67 ± 21.06    | 52.78 ± 21.08    |
| Physical Functioning     | 80.52 ± 22.43    | 84.26 ± 10.57    |
| Pain                     | 74.06 ± 32.86    | 72.83 ± 24.90    |
| Health Distress          | 80.00 ± 24.23    | 70.55 ± 31.57    |
| Health Transition        | 66.67 ± 25.00    | 61.11 ± 18.16    |
| Energy/Fatigue           | 58.89 ± 19.12    | 58.89 ± 23.15    |
| Role Functioning         | 66.67 ± 35.35    | 77.78 ± 36.32    |
| Social Functioning       | 82.22 ± 32.31    | 75.55 ± 29.62    |
| Cognitive Functioning    | 77.22 ± 19.70    | 75.55 ± 14.01    |
| Mental Health            | 74.22 ± 19.12    | 69.67 ± 20.37    |
| Self-Efficacy for Exercise | 64.22 ± 17.00 | 53.66 ± 13.49   |

All values are expressed as mean ± standard deviation
*Significant difference between groups (P = 0.04)
a. Measured via computer homeostatic model assessment
### Table 2. Exercise Prescription Data forCompleters (n=9)

<table>
<thead>
<tr>
<th>Participant</th>
<th>Compliance</th>
<th>Range</th>
<th>Average</th>
<th>Range (mins)</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>H014-12</td>
<td>72%</td>
<td>50-80%</td>
<td>60%</td>
<td>20-32</td>
<td>26.57</td>
</tr>
<tr>
<td>H014-13</td>
<td>83%</td>
<td>75-80%</td>
<td>80%</td>
<td>20-40</td>
<td>29.00</td>
</tr>
<tr>
<td>H013-17</td>
<td>92%</td>
<td>60-75%</td>
<td>75%</td>
<td>20-40</td>
<td>28.50</td>
</tr>
<tr>
<td>H014-20</td>
<td>70%</td>
<td>50-65%</td>
<td>65%</td>
<td>20-40</td>
<td>29.48</td>
</tr>
<tr>
<td>H014-23</td>
<td>83%</td>
<td>75-80%</td>
<td>75%</td>
<td>20-40</td>
<td>29.31</td>
</tr>
<tr>
<td>H014-24</td>
<td>36%</td>
<td>50-60%</td>
<td>55%</td>
<td>20-26</td>
<td>23.66</td>
</tr>
<tr>
<td>H014-28</td>
<td>55%</td>
<td>55-60%</td>
<td>60%</td>
<td>20-32</td>
<td>26.44</td>
</tr>
<tr>
<td>H014-29</td>
<td>83%</td>
<td>55-75%</td>
<td>65%</td>
<td>20-40</td>
<td>28.71</td>
</tr>
<tr>
<td>H014-30</td>
<td>58%</td>
<td>75-80%</td>
<td>80%</td>
<td>20-34</td>
<td>26.57</td>
</tr>
</tbody>
</table>

### Table 3. Demographic, Physical, and Clinical Characteristics for Completers (n=9) at Entry and 12 wks

<table>
<thead>
<tr>
<th></th>
<th>Entry</th>
<th>12 Wks</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4+ (cel.mm-3)</td>
<td>520.00 ± 215.92</td>
<td>489.11 ± 234.04</td>
<td>0.20</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>76.52 ± 13.82</td>
<td>76.11 ± 12.55</td>
<td>0.40</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>27.46 ± 6.14</td>
<td>27.97 ± 6.04</td>
<td>0.21</td>
</tr>
<tr>
<td>VO2max (mL/kg-1/min-1)</td>
<td>33.71 ± 10.30</td>
<td>34.66 ± 7.99</td>
<td>0.35</td>
</tr>
<tr>
<td>Triglycerides (mg.dL-1)</td>
<td>122.67 ± 50.83</td>
<td>102.33 ± 40.28</td>
<td>0.03*</td>
</tr>
<tr>
<td>Total cholesterol (mg.dL-1)</td>
<td>174.33 ± 19.78</td>
<td>168.00 ± 19.14</td>
<td>0.16</td>
</tr>
<tr>
<td>HDL cholesterol (mg.dL-1)</td>
<td>55.56 ± 15.53</td>
<td>54.22 ± 0.69</td>
<td>0.34</td>
</tr>
<tr>
<td>LDL cholesterol (mg.dL-1)</td>
<td>95.22 ± 25.84</td>
<td>93.33 ± 26.70</td>
<td>0.32</td>
</tr>
<tr>
<td>Non-HDL cholesterol (mg.dL-1)</td>
<td>118.78 ± 0.12</td>
<td>113.78 ± 30.56</td>
<td>0.10</td>
</tr>
<tr>
<td>Insulin (mg.dL-1)</td>
<td>11.21 ± 10.52</td>
<td>9.26 ± 7.31</td>
<td>0.15</td>
</tr>
<tr>
<td>Glucose (mg.dL-1)</td>
<td>93.33 ± 17.10</td>
<td>92.44 ± 8.19</td>
<td>0.41</td>
</tr>
<tr>
<td>Insulin Sensitivity (%)</td>
<td>99.43 ± 61.76</td>
<td>106.90 ± 55.31</td>
<td>0.28</td>
</tr>
</tbody>
</table>

All values are expressed as mean ± standard deviation and P values. *P <0.05 for comparison within group.

### Table 4. Quality of Life (MOS-HIV) Data for Completers at Entry and 12 wks (n=9)

<table>
<thead>
<tr>
<th>MOS-HIV</th>
<th>Entry</th>
<th>12 Wks</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of Life</td>
<td>75.00 ± 17.67</td>
<td>72.22 ± 15.02</td>
<td>0.34</td>
</tr>
<tr>
<td>General Health Perception</td>
<td>66.67 ± 21.06</td>
<td>69.44 ± 18.78</td>
<td>0.14</td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>80.52 ± 22.43</td>
<td>84.26 ± 20.60</td>
<td>0.31</td>
</tr>
<tr>
<td>Pain</td>
<td>74.06 ± 32.86</td>
<td>56.79 ± 8.68</td>
<td>0.06</td>
</tr>
<tr>
<td>Health Distress</td>
<td>80.00 ± 24.23</td>
<td>78.89 ± 14.96</td>
<td>0.43</td>
</tr>
<tr>
<td>Health Transition</td>
<td>66.67 ± 25.00</td>
<td>88.89 ± 13.17</td>
<td>0.02*</td>
</tr>
<tr>
<td>Energy/Fatigue</td>
<td>58.89 ± 19.12</td>
<td>59.44 ± 18.95</td>
<td>0.47</td>
</tr>
<tr>
<td>Role Functioning</td>
<td>66.67 ± 35.35</td>
<td>72.22 ± 50.69</td>
<td>0.36</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>82.22 ± 32.31</td>
<td>75.55 ± 32.83</td>
<td>0.35</td>
</tr>
<tr>
<td>Cognitive Functioning</td>
<td>77.22 ± 19.70</td>
<td>80.00 ± 14.14</td>
<td>0.30</td>
</tr>
<tr>
<td>Mental Health</td>
<td>74.22 ± 19.12</td>
<td>71.11 ± 22.51</td>
<td>0.38</td>
</tr>
</tbody>
</table>

All values are expressed as mean ± standard deviation and P values. *P <0.05 for comparison within group.
<table>
<thead>
<tr>
<th></th>
<th>Compliers</th>
<th>Non-Compliers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attraction to Group - Task</td>
<td>6.83 ± 1.33</td>
<td>8.33 ± 2.52</td>
</tr>
<tr>
<td>Attraction to Group - Social</td>
<td>13.17 ± 7.52</td>
<td>30.67 ± 21.57</td>
</tr>
<tr>
<td>Group Integration - Task</td>
<td>11.00 ± 9.57</td>
<td>14.67 ± 14.22</td>
</tr>
<tr>
<td>Group Integration - Social</td>
<td>21.33 ± 8.52</td>
<td>17.67 ± 12.34</td>
</tr>
</tbody>
</table>

All values are expressed as mean ± standard deviation
DISCUSSION

Currently, no specific guidelines exist for exercise prescription in people living with HIV. It was hypothesized that a group-based program conducted at a convenient location and led by trained professionals would increase exercise adherence based on positive results from other group interventions [19, 20]. Surprisingly, our attempt to increase adherence via group activities replicated results from other exercise interventions conducted with HIV-negative [38, 39] as well as HIV+ individuals [10, 12, 40] with a 50% drop-out rate.

On average “non-completers” (n=9) attended only six exercise sessions and withdrew from the study during the first two weeks of the exercise program. Non-completers were significantly less fit than completers (n=9) at entry ($P=0.04$). Though not statistically significant, those who completed the exercise intervention had higher self-efficacy scores at entry than those who did not ($P=0.08$). Self-efficacy is defined as “the belief that one can successfully perform a desired behavior given various instrumental barriers” [41] and was measured at entry with the Self-Efficacy for Exercise Scale (SEE) [30]. Self-efficacy has been cited as an important factor that contributes to adherence to treatment [40], therefore low level SEE scores in the non-completers may help to explain their withdrawal from the exercise intervention.

Significant pre to post differences were revealed in triglyceride level ($P=0.03$) and health transition scores ($P=0.02$) in the MOS-HIV among the “completers” (n=9). Triglyceride levels decreased ($P=0.03$) throughout the course of the present study. This is consistent with findings from other aerobic exercise intervention studies and is not
surprising [9, 42, 43] since triglyceride metabolism is known to increase during and following physical activity, induced by changes in enzyme levels [12].

While triglyceride levels significantly decreased in this study, there were no remarkable differences in total cholesterol, LDL or HDL levels, insulin, glucose, insulin sensitivity, or body composition. Previous studies employing aerobic exercise programs [12, 14] as well as combined aerobic and resistance training protocols [8, 10] also found that metabolic parameters remained unchanged despite increases in cardiorespiratory fitness. One possible explanation for the lack of change in metabolic parameters in the present study is that we did not specifically recruit patients who had metabolic syndrome, lipodystrophy or dyslipidemia; only one participant met the International Diabetes Federation criteria for metabolic syndrome [44].

Despite the lack of statistical significance among the completers, the aforementioned participant underwent clinically significant changes throughout the course of the exercise intervention. This 46 yr old Caucasian male who had been living with HIV for 27 years presented with metabolic syndrome and weighed 223 lbs, had dyslipidemia, and fasting glucose levels in the diabetic range. During the exercise intervention he lost 21 lbs, (android fat dropped from 51.5 to 48 %) and improved in the following metabolic parameters: total cholesterol 190 – 162 mg/dL, triglycerides 190 - 120 mg/dL, insulin 34.6-18.9 mg/dL, glucose 135 – 112 mg/dL, and insulin sensitivity 21.3 – 39.4%.

Among the completers a significant improvement ($P=0.02$) from entry to 12 wks was revealed in the Health Transition dimension of the MOS-HIV, utilized to measure health related quality of life. Low scores in this dimension indicated that the patients’
physical health and emotional condition were much worse prior to program entry (4 wks), and were much better after the exercise intervention as indicated by their higher scores. Consequently, completers felt better regarding their overall physical and emotional condition at the conclusion of 12 wks of exercise. Completers’ health related quality of life did not change remarkably from entry to 12 wks for any other dimension, contrary to previous studies which showed improvement in quality of life outcomes [11, 45]. Since completers began this study with fairly favorable scores in health related quality of life dimensions, similar to those of other asymptomatic HIV+ cohorts [46, 47], further improvements were limited. Figure 1 presents the comparison of MOS-HIV dimension scores at entry for the present study as well as two other asymptomatic HIV+ cohorts.

Only six of the completers were considered compliant (compliers, n=6), attending more than 70% of the exercise sessions. This sub-group demonstrated significant improvements in VO\textsubscript{2max} values (\(P=0.03\)) during the exercise intervention. These
findings show that compliance to this 12 wk aerobic exercise program sufficiently challenged the cardiorespiratory system without depressing immune function (CD4 or viral load). On average $\text{VO}_{2\text{max}}$ levels increased by 15% in compliers; this increase in fitness level is comparable to other aerobic exercise intervention studies conducted with medically stable HIV+ patients [8, 11, 12]. However, this exercise prescription may not be appropriate for patients in more advanced disease stages.

Numerous factors contribute to exercise compliance. Satisfaction with the exercise instructor is one variable that has been shown to have an affect on compliance in exercise programs [48]. Completers filled out an evaluation on the exercise instructor at the conclusion of the program. This six-item Likert scale questionnaire involved responding to a statement with answers ranging from “strongly disagree to strongly agree”. Statements included the exercise instructor was: knowledgeable, clear, enthusiastic, showed interest in participants, supportive, and appeared fit. No difference was seen between compliers and non-compliers; the mode response for all statements was strongly agree. Therefore, satisfaction with the exercise instructor did not appear to be a contributing factor to compliance for those who completed the exercise program.

Cohesion is an important factor to consider in group-based exercise. Group cohesion has consistently been found to predict compliance behaviors within the context of group-based exercise programs [28] and is defined as “a dynamic process that is reflected in the tendency for a group to stick together and remain united in the pursuit of its instrumental objectives and/or for the satisfaction of member affective needs” [49]. The Physical Activity Group Environment Questionnaire (PAGEQ) measured group cohesion in the present study. Compliers demonstrated higher levels of cohesion for
three of the four subscales in the PAGEQ. This difference may be due to the fact that recruitment was rolling and participants entered the study at different times.

Subsequently, participants (n=18) were in different phases (exercise intensity and duration) of the exercise program upon entry which limited group interaction throughout the course of the study. Interestingly, five out of six of the compliers were enrolled at approximately the same time and went through much of the 12 wk exercise program together.

Within the limitations of the study, a 12 wk group-based aerobic exercise program resulted in improvements in triglyceride levels and cardiorespiratory fitness among compliers and had no negative effect on immune function in HAART treated HIV+ individuals. The small sample size and high drop-out rate in the present study could have compromised the ability to detect differences within the group. Furthermore, results from this study were based on a relatively homogenous sample of participants and can only be applied to HIV+ middle-aged males. Regardless of these limitations, the exercise prescription utilized in this study was well tolerated and did not result in any adverse events throughout the course of the study. Therefore, supervised group-based aerobic exercise programs are a viable adjunct treatment option for the negative effects of HIV and HAART medications.
Part II

REVIEW OF LITERATURE

Metabolic Disorders Associated with HIV and HAART

Highly Active Antiretroviral Therapy (HAART) has minimized Human Immunodeficiency Virus (HIV) replication and improved immune function, which has reduced mortality rates [50] and extended life expectancy [50]. HAART is defined as the combination of three or more antiretroviral medications from at least two different classes [51]. Antiretroviral drugs fall into six classes: protease inhibitors (PIs), non-nucleoside reverse-transcriptase inhibitors (NNRTIs), nucleoside reverse-transcriptase inhibitors (NRTIs), integrase inhibitors, fusion inhibitors, and CCR5 antagonists [2, 3]. Most antiretroviral regimens are built around an NRTI, NNRTI, or PI [3]. Nucleoside reverse-transcriptase inhibitors require intracellular activation and are incorporated into the growing deoxyribonucleic acid (DNA) strand by HIV reverse transcriptase, subsequently preventing further reverse transcription. Non-nucleoside reverse-transcriptase inhibitors (NNRTIs) have helped to simplify antiretroviral regimens as their pharmacokinetic profile permits once or twice daily administration and they do not require intracellular activation. Protease Inhibitors (PIs) block HIV protease, an enzyme responsible for post-translational cleavage of viral polyprotein precursors into smaller, mature proteins. As a result immature, non-infectious virions are produced [51].

Though HAART has significantly enhanced the management and clinical outcome of HIV, these favorable effects have been limited by the development of metabolic disorders including insulin resistance, diabetes mellitus, and dyslipidemia as well as body shape changes [52]. Initially, these changes were assumed to be associated
with HAART [52]. However, infection with HIV itself, regardless of the initiation of
HAART, may cause a number of significant anthropometric and metabolic alterations,
including wasting, dyslipidemia, osteoporosis, hepatic lipogenesis, and changes in the
immunologic and cytokine systems, even though underlying mechanisms are not
completely understood [3, 51].

Antiretroviral drugs themselves affect adipocyte function at the molecular level.
Subsequently, the body’s response to these alterations plays a role in the pathogenesis of
lipoatrophy or the loss of peripheral fat in the face, limbs, and buttocks [53]. Adipocyte
toxicity resulting from the use of PIs and NRTIs results in cellular dysfunction, and in the
case of mitochondrial toxicity, decreased oxidative capacity [5, 54]. Increased free
radical activity initiates cellular damage and the release of pro-inflammatory cytokines
which leads to additional loss of adipocytes and accelerated lipoatrophy [3].
Lipohypertrophy or central adiposity occurs as part of a compensatory process for
lipoatrophy. Excess circulating lipids and glucose, which would normally be stored in
peripheral adipose tissue, are taken up by other tissues [55]. While lipohypertrophy is
typically found in HAART experienced HIV-infected patients, it has been noted to occur
regardless of the use of PIs [3].

Dyslipidemia is closely related to the anthropometric changes described above
and has a multifaceted pathogenesis with HIV infection, antiretroviral drugs (in particular
PIs), diet, and genetic factors all contributing to its’ development [51]. Decreases in high
density lipoprotein (HDL) and increases in total cholesterol and triglyceride levels have
been shown to occur in antiretroviral naïve patients demonstrating that HIV infection
itself may be a potential cause [51]. However, it has also been well established that
dyslipidemia is associated with many antiretroviral regimens [56]. While the exact mechanism is not clear, the decrease in HDL cholesterol may be the result of disruption of reverse cholesterol transport in circulating monocytes and tissue macrophages [51]. Changes in cholesterol and triglyceride levels can occur early in therapy, prior to any changes in body composition. Once body composition alterations are established, there is decreased clearance of excess lipoproteins from the circulation as subcutaneous adipose tissue normally acts as a buffer for dietary lipids. In addition, there is less available storage for circulating lipids in the case of lipoatrophy, thereby exacerbating the increased cholesterol and triglyceride levels.[3]

Insulin sensitivity is indirectly affected by changes in lipid metabolism and adipose tissue and directly affected by some PIs [57]. Lipoatrophy removes the potential to store dietary lipids and glucose in subcutaneous fat which leads to an accumulation of excess lipids in other tissues and organs which results in insulin resistance. In addition, subcutaneous adipose tissue secretes the hormones leptin and adiponectin, which are both involved in the regulation of insulin sensitivity.[51] HIV infection itself may independently be linked to the attenuation of insulin sensitivity as well [57].

In some HIV-infected individuals exposed to NRTIs, lipoatrophy predominates in conjunction with lactic acidemia, which reflects NRTI-induced mitochondrial dysfunction [3]. Decreased mitochondrial function results in disruption of intracellular oxidative capacity, which causes the cell to rely more heavily on anaerobic metabolism, the end product of which is lactate. Patients with mild to moderate lactic acidemia experience fatigue, anorexia, weight loss, gastrointestinal symptoms, and often have liver function test abnormalities [51]. Patients with lactic acidosis may present with a sepsis-
like syndrome, myopathy, or peripheral neuropathy. Once metabolic de-compensation occurs, widespread end-organ damage rapidly follows [4].

Collectively, the previously described dysfunctions are termed HIV-1/HAART-associated metabolic syndrome or HIV-1 associated lipodystrophy. The term HIV-1 associated lipodystrophy focuses more on the morphological changes [4, 5] including wasting of peripheral subcutaneous fat (face, limbs, and buttocks), and accumulation of central visceral fat (cervicodorsal region, breasts, and abdomen) [3]. Metabolic abnormalities associated with lipodystrophy include dyslipidemia, insulin resistance, diabetes mellitus, and lactic acidemia.

Metabolic syndrome prevalence was recently assessed in a cross-sectional study which included a large international cohort (n=788) of HIV-infected patients. Metabolic syndrome was defined using the International Diabetes Federation (IDF) and U.S. National Cholesterol Education Program Adult Treatment Panel III (ATPIII) criteria. IDF criteria are waist circumference > 80 cm in women and > 94 cm in men plus two of the following: triglycerides > 1.7 mmol/l, HDL <1.29 mmol/l, glucose > 5.6 mmol/l, systolic blood pressure >130 mmHg, or diastolic blood pressure > 85 mmHg (17). ATPIII criteria are three of the following: waist circumference > 88 cm in women and > 102 cm in men, triglycerides > 1.7 mmol/l, HDL < 1.20 mmol/l in women or > 1.0 mmol/l in men, glucose > 6.1 mmol/l, or blood pressure >130/85 mmHg. The prevalence of metabolic syndrome in this cohort was found to be 14–18%, depending on the criteria used, which is less than that of the general adult population in the U.S. (24%). However, 49% of patients met two of the three criteria for metabolic syndrome, but were not
classified as such due to waist circumferences or waist-to-hip ratios falling in the non-metabolic range.[4]

The development of metabolic syndrome in HIV-infected individuals is important to address in that it results in a potential increased risk for cardiovascular disease and diabetes [7]. Even after adjustment for age, sex, cholesterol level, physical activity, and smoking, metabolic syndrome was found to double coronary heart disease mortality [58-60]. In addition, metabolic syndrome has been associated with a five to eight fold increased diabetes prevalence [59, 60].

**Manifestation of Metabolic Disorders in Exercise**

The direct measurement of oxygen uptake and carbon dioxide production through cardiopulmonary exercise testing can be used to determine exercise intolerance and the underlying causes including limitations of the ventilatory, cardiovascular, or muscular systems. In addition, subtle indicators of de-conditioning and training-induced adaptations can be ascertained from data gathered during cardiopulmonary exercise testing. Maximal oxygen uptake (VO$_{2\text{max}}$) is the gold standard measurement of exercise capacity and reflects oxygen delivery by the cardiorespiratory system and oxygen utilization by the exercising muscles.[12, 43, 61]

It has been well-established that HIV-infected persons display decreased functional aerobic capacity (FAC) [11], as well as functional aerobic impairment (FAI) or peak VO$_2$ less than 73% of expected values [11]. The specific mechanism underlying FAI remains unclear. However, FAI has been shown to be eliminated through aerobic training regimens [60]. The role of de-conditioning has been proposed as a contributor to
aerobic dysfunction in those infected with HIV [59]. Stringer et al. concluded that decreased aerobic capacity seen in HIV-infected patients was the result of de-conditioning based on the fact that aerobic capacity improved with exercise training [62]. This theory was refuted by results from another study in which sedentary HIV-infected adolescents performed a graded maximal exercise test and were directly compared to a control group who reported similar physical inactivity. Functional aerobic impairment, a condition associated with severe pathological attenuation of the oxidative metabolic pathway, was identified in the subjects who were infected with HIV and not the control group. Therefore, authors concluded that diminished aerobic capacity in HIV-infected individuals was due to other factors besides physiologic de-conditioning.[63]

To further elucidate the mechanisms for decreased aerobic capacity seen in HIV-infected individuals, the same group conducted a study with 15 HIV-infected adults and HIV-negative controls in which an incremental maximal exercise test was given. Peak VO$_2$ and arteriovenous oxygen difference ($a$-VO$_2$) was significantly lower in participants with HIV as compared with controls. Arteriovenous oxygen difference has been generally accepted as a gross indicator of tissue oxygen extraction and utilization and closely reflects oxidative function of muscle tissue, particularly when measured during strenuous exercise. As there were no significant intergroup differences in cardiac output or stroke volume at peak exercise the observed deficit in aerobic capacity in the participants with HIV appeared to be the result of a peripheral tissue oxygen extraction or utilization limitation. In addition to de-conditioning, potential mechanisms for this significant attenuation may include HIV infection and inflammation, HAART, or a combination [7].
Duong et al. evaluated exercise and oxidative capacities as well as circulatory and ventilatory responses to exercise in 24 HIV-infected patients on NRTIs presenting with hyperlactataemia. Twenty-seven NRTI-treated patients with normal baseline lactate concentrations were used as controls. In the patients with hyperlactataemia, the average peak work capacity and peak oxygen consumption were significantly lower than in control subjects. The capacity to increase oxygen extraction during exercise was significantly diminished in the hyperlactataemia group, as shown by a low peak systemic arteriovenous oxygen difference compared with controls, and as indicated by a linear correlation between $VO_2$ and systemic a-VO$_2$. The degree of exercise limitation in patients with nucleoside-related mitochondrial toxicity correlates directly with the severity of impaired muscle oxidative phosphorylation, as indicated by the capacity for muscle oxygen extraction. Exaggerated circulatory and ventilatory responses to exercise are direct consequences of the level of impaired muscle oxidative phosphorylation as they are the predominant regulatory mechanisms to compensate for the imbalance in the normal coupling between $O_2$ delivery and utilization. HIV-infected patients with nucleoside-related mitochondrial toxicity have significant exercise limitations, which result from reduced capacity for muscle oxygen extraction. Lactate concentration at peak exercise was similar in the two groups, lactate levels were high relative to peak workload and $VO_2$ in hyperlactatemia patients compared with controls.[6] This finding was consistent with results from another study conducted on HIV-negative patients with mitochondrial disorders. Peak concentrations of blood lactate were similar to controls and not pronounced, however, lactate accumulation continued after the exercise.[64]
Exercise Mediation

HIV infection and HAART regimens result in a host of metabolic and anthropometric side effects which have relevance to exercise, including muscle wasting, adipose tissue redistribution, lipid abnormalities, insulin resistance or glucose intolerance, mitochondrial abnormalities, and hyperlactatemia. Exercise training and physical activity are well-known to reduce central adiposity, blood lipids, and carbohydrate disorders in people who are HIV-negative [6, 64]. It has been established that an increase in aerobic performance capacity, both in healthy subjects and cardiac patients, leads to an elevation of HDL and a reduction in very low-density lipoproteins (VLDL) and low-density lipoproteins (LDL) cholesterol, as well as triglycerides [64]. Changes in body weight and composition may contribute to the lipid and lipoprotein response to physical training as in most studies LDL levels do not appear to lower after aerobic exercise unless there is a concomitant body composition change. However, most studies have evaluated subjects with normal LDL levels and few have assessed those at high risk. Most prospective training studies indicate that endurance exercise raises HDL levels [42]. Potential mechanisms of action of exercise in lipid and lipoprotein metabolism may be explained by the effect of training on enzymes involved in lipoprotein metabolism. There is an increased metabolism of triglycerides during and following physical activity induced by changes in enzyme levels. Increased lipoprotein lipase activity and decreased hepatic lipase activity is associated with exercise and results in lower triglyceride levels and higher HDL concentrations.[12]

Physical activity also affects both hepatic glucose output and glucose uptake by exercising muscle in normal individuals. Regular physical activity has led to consistent
improvements in long-term indicators of glycemic control among patients with type II diabetes which is characterized by insulin resistance and impaired insulin secretion. In addition, physical training may alter glucose homeostasis by increasing insulin sensitivity. However, the mechanism of increased insulin sensitivity is not understood completely. The amount of glycogen storage in skeletal muscle is decreased in those with diabetes. Regular exercise counteracts this effect by increasing skeletal muscle enzyme activity which will augment glucose uptake and re-synthesis of muscle glycogen stores.[65]

Health benefits associated with exercise in the HIV-negative population are well known. Subsequently, exercise may be a promising treatment for the side effects of HIV and HAART for patients who do not wish to add more medications to an already complicated and extensive drug regimen. Recently, authors have sought to evaluate whether or not HIV-infected individuals respond in the same manner as their healthy counterparts.

A 16 week purely aerobic cycling program administered in lipodystrophic adults resulted in improvements in body composition and blood lipids. Data were analyzed with paired t-tests or the Wilcoxon test when appropriate. Total cholesterol and triglycerides all significantly decreased whereas HDL increased. The exercise program consisted of 2 supervised sessions a week lasting 45 minutes on a cycle ergometer at a heart rate which corresponded to ventilatory threshold as determined by a maximal graded exercise test. [9].

Conversely, a 12 week exercise or stretching intervention study which evaluated 30 HIV-infected individuals with dyslipidemia and lipodystrophy failed to alter plasma
triglycerides, total cholesterol, and HDL cholesterol levels. Participants, who were all on protease inhibitors and/or non-nucleoside reverse transcriptase inhibitors, were randomly assigned to an aerobic exercise or stretching and relaxation program. The aerobic exercise protocol was performed 3 times per week for one hour. All sessions were supervised by one of the investigators. Each session began with a 15 minute stretch / warm-up period, followed by 30 minutes of running at 70-85% of heart rate max determined by the initial exercise test. The control group met with the same frequency and duration as the exercise group, however, sessions included soft stretching and relaxation routines with no heart rate elevation which accounted for co-intervention. Participants also received recommendations for a low-lipid diet. Outcome measures included peak oxygen uptake, body composition, CD4 levels, viral load, lipid profile, and plasma endothelin-1 levels. Peak oxygen uptake increased significantly in the diet and exercise but not in the diet only group. Statistical analysis included a two way ANOVA with repeated measures to examine the effect of the interventions. Body weight, body fat, and waist-to-hip ratio decreased significantly and similarly in the two groups. There were no significant changes in immunologic variables in either group. Likewise, plasma triglycerides, total cholesterol, and HDL cholesterol levels did not change significantly in either group. Authors concluded that HIV-seropositive individuals with lipodystrophy and dyslipidemia submitted to 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. [14]

A long term study was conducted by Birk et al. to determine the effects of 12 months of aerobic exercise training on blood lipid and lipoprotein concentrations in 5
men with advanced HIV infection. The exercise regimen was conducted 3 times a week for 40 minutes at 60 – 70% of VO$_{2max}$. A general linear model with multivariate analysis was used to determine whether significant changes resulted in the pre to post-lipid/lipoprotein dependent variables within and between the five subjects over the 12 month study. A significant increase in triglyceride concentration was observed, while there was no significant difference between cholesterol, and HDL concentrations. The lack of significance may be ascribed to the small sample size (only 4 of the participants were more than 80% compliant) and lack of sufficient intensity.[43]

A study conducted by Lindegaard et al. evaluated the effects of endurance and resistance training on insulin sensitivity and lipodystrophy in HIV positive men. Participants were randomly assigned to either the strength or endurance training 3 times a week for 16 weeks. Only strength training increased total lean mass, decreased total fat, trunk fat, and limb fat. Endurance training reduced total cholesterol, low-density lipoprotein cholesterol, free fatty acids, high sensitivity C-reactive protein, IL-6, IL-18, and TNF and increased high-density lipoprotein cholesterol, whereas strength training decreased triglycerides, free fatty acids, and IL-18 and increased HDL. Both endurance and strength training increased insulin-mediated glucose uptake which was contrary to previous findings. Authors attributed this difference to the use of indirect methods of measurements used in previous studies. Authors concluded that both strength and endurance training improve peripheral insulin sensitivity, whereas only strength training reduces total body fat in HIV-infected patients with lipodystrophy.[10]

The effects of combined aerobic and progressive resistance training programs on metabolic markers have also recently been evaluated in the HIV-infected population. A
study conducted by Grinspoon et al. evaluated the independent effects of testosterone therapy and progressive resistance training (3 times weekly for 12 weeks) in eugonadal men with AIDS wasting. During each session, patients began by performing 20 minutes of aerobic exercise on a stationary bicycle at 60 – 70% of their age-predicted maximum. A cool-down period of 15 minutes preceded resistance training, which was performed isotonically targeting the large muscle groups. A 2X 2 ANOVA was utilized to evaluate the effects of testosterone and resistance training on body composition, muscle strength, hormone and lipid levels, and immune function. Both treatments improved muscle strength, however, the resistance training group had a significant increase in HDL levels while the testosterone group decreased over the course of the study. Authors concluded that exercise may be an ideal strategy to reverse muscle loss in these specific patients. [8]

Additionally, 6 HIV-infected individuals with lipodystrophy decreased total cholesterol, triglyceride concentrations, and subcutaneous fat over the course of a 10 week combined program. HDL demonstrated a small increase, which when combined with reductions in total cholesterol, resulted in a 23% reduction in the total cholesterol: HDL ratio. The exercise program consisted of 90 minute sessions performed 3 times a week. Each session included 20 minutes of cycling at 70% of pear heart rate, followed by 60 minutes of resistance training.[8]

A pilot study evaluated the effects of a combined program over the course of 16 weeks in 5 HIV-infected adults. Nine participants were recruited to participate in the study. Each exercise session consisted of 20 minutes of aerobic exercise training; walking, jogging, or running on a treadmill at 70 – 80% of VO_2Max. Two of the three endurance training sessions were immediately followed with resistance training which
consisted of one set of 8 – 10 reps of 7 exercises performed at 80% of participants’ 1 RM. Outcome measures included lipid levels, visceral and subcutaneous adipose area, fat and lean mass of trunk and limbs, and insulin sensitivity. Only 5 of the 9 participants completed the 16 week exercise program. Aerobic capacity and strength improved over the course of the program. There were significant decreases for total and trunk fat mass. Triglycerides and insulin sensitivity both decreased, but not significantly. As this was a pilot study and only 5 participants completed the intervention, authors concluded that further study is warranted on combined exercise in a randomized controlled trial. [66]

Another combined program sought to evaluate the effects of a 12 week home-based supervised exercise regimen in 40 HIV-infected women with increased waist-hip ratio and self-reported fat redistribution. There were no significant differences in lipid levels, blood pressure, or abdominal visceral fat between the exercise and control groups after the course of the study. The strongest findings from this study were the positive effects of resistance training on strength, however positive effects on cardiorespiratory fitness, body composition, and endurance were also seen. The lack of differences in lipid and glucose levels may be due to the small sample size and limited aerobic stimulus [7]. Participants in this study began aerobic exercise at 50% of their estimated VO\(_{2\text{max}}\) and gradually progressed to 75% whereas the aforementioned studies utilized higher training intensities. [33]

The effects of exercise used in tandem with medications has been evaluated in a prospective randomized controlled trial on the effects of receiving the diabetic drug metformin alone or in combination with 12 weeks of exercise training in 25 HIV-infected patients with fat redistribution and insulin resistance. The exercise protocol consisted of
20 – 30 minutes of aerobic exercise at 60-75% of maximal heart rate followed by resistance training. Researchers found that exercise plus metformin resulted in greater reductions in waist-to-hip ratio, thigh adiposity, blood pressure, and fasting insulin, and larger increases in muscle area and exercise time compared with participants receiving metformin alone. Neither intervention altered blood lipid levels. The absence of an effect on blood lipids may relate to the unique pathophysiology of lipid abnormalities in HIV infection or an ongoing effect of antiretroviral treatment that may prevent positive training-induced adaptations of lipid metabolism in some individuals.[8, 14, 15, 20, 67, 68]

It remains inconclusive whether exercise and physical activity have the same benefits for people with HIV as their healthy counterparts [15]. Intervention studies that evaluated the effects of exercise training on metabolic outcomes in this population are in their infancy. These studies also have a number of methodological limitations, including lack of a non-exercising control group, small sample sizes, short training durations, and variable criteria used to define lipodystrophy or metabolic syndrome. However, positive outcomes indicated in many of these studies warrant larger more rigorous controlled studies.

Exercise Prescription

To increase cardiorespiratory fitness the American College of Sports Medicine (ACSM) recommends exercise intensities of 40 – 85% of oxygen consumption reserve (VO\textsubscript{2r}) which is the difference between resting VO\textsubscript{2} and VO\textsubscript{2\textsubscript{max}}. Moderate intensity exercise is defined as 40 – 59% of VO\textsubscript{2r} and vigorous intensity as > 60%.[15] When
exercise research first began to emerge in the early 1990’s there was concern surrounding a possible immunosuppression effect in HIV-infected individuals, specifically with high intensity exercise. Results from studies conducted at low to moderate intensities, 50-85% \( VO_{2\text{max}} \) or Max HR, showed that exercise does not increase the prevalence of additional infections, increase viral load, nor does it decrease CD4+ T-cell count [69]. One study specifically addressed the effect of moderate and high intensity exercise on immune function, prescribing the moderate intensity group to work at 80% of their lactic acidosis threshold (LAT) work rate and the high intensity group performed training equal to 50% of the difference between their LAT and their \( VO_{2\text{max}} \) [11, 70]. When directly compared there were no differences between groups, and no overall negative effect on immune indices [8, 9, 12, 66]. Several studies have even reported increased immune function, particularly in asymptomatic participants. However, these responses are not consistent and remain controversial [33]. As there have been no adverse events related to high intensity exercise, it has been deemed safe for this population. In fact, it seems the most marked improvements in aerobic function and quality of life occur with high intensity exercise training relative to a control group [69]. While it appears that a wide range of exercise intensities are safe to use in this population it would be unwise to neglect the possibility of immune system suppression when prescribing exercise. Over training must be a serious concern and care should be taken to monitor individual responses.

The majority of exercise interventions conducted in the HIV-infected population have used some form of equipment for administration of aerobic exercise such as treadmills, cycle ergometers, or ski machines [33]. Reliable measures of energy expenditure are obtained from these cardiorespiratory activities and are not significantly
affected by age, sex, or skill [19]. These types of activities are also advantageous when it is important to regulate and maintain intensity throughout exercise. The ability to control exercise intensity is vital to the safety of the exercise program, especially when working with a diseased population [33]. While aerobic exercise completed on equipment has its advantages, it is often limited to administration on an individual basis. One major limitation of exercise research in HIV-infected individuals is the high drop-out rates associated with these trials. Group exercise has been suggested as one strategy to promote adherence to exercise prescription in the HIV-infected population [8-10, 12, 61, 68] as it adds a socialization context for participants [33]. Having participants walk or run in groups continues to offer the advantages described above and may result in higher rates of adherence.

To improve cardiorespiratory fitness for apparently healthy adults, the recommended frequency of exercise sessions range from 3 – 7 days a week [8-10, 12, 15, 67, 68]. The majority of exercise interventions conducted in the HIV-infected population have utilized a 3 day per week training schedule [67]. This frequency is in accordance with recommendations from the ACSM for sedentary individuals initiating an exercise program which is prudent considering inclusionary criteria for most of these studies require that participants be minimally active prior to the start of the study. Additionally, it is also more feasible for participants to complete 3 exercise sessions a week. None of the identified studies increased sessions per week throughout the training program. However, all programs produced significant improvements in VO$_{2\text{max}}$ or VO$_{2\text{peak}}$ indicating that this frequency was sufficient to produce improvements in
cardiorespiratory fitness levels in this population. Prescribing exercise for 3 days a week has been proven to be feasible, safe, and effective in this population.

Exercise duration to achieve improvement in cardiorespiratory fitness ranges from 20 – 60 minutes [12]. When reviewing protocols implemented in this population, the aerobic portion of the exercise session has been prescribed for 20 to 35 minutes [8-11, 68]. Only one study required participants to exercise at the minimum requirement of 20 minutes over the course of 15 weeks [7]. Incidentally this was the only study reviewed in which there was no significant change in VO$_{2\text{max}}$. Initiating a program with 20 minutes of aerobic exercise and progressing to 30 minutes after several weeks has been shown to result in increases in cardiorespiratory fitness [71]. Other than the two previously mentioned studies, the remainder of interventions reviewed utilized 30 minutes of aerobic exercise which increased fitness levels and produced no adverse events [71]. In regards to exercise duration it appears that 30 minutes is a fairly reasonable amount of time to prescribe to HIV-infected individuals. Less than that appears to be ineffective, and more could prove to be detrimental to health as prolonged aerobic exercise has not yet been studied.

To date, no specific guidelines exist for exercise prescription in people living with HIV. However, the aerobic exercise programs prescribed in previous exercise intervention studies appear to be safe among adults with HIV who are medically stable. It is important to re-iterate the fact that participants studied in prior exercise research were medically stable, very few had progressed to the diagnosis of Acquired Immune Deficiency Syndrome (AIDS). Therefore recommendations cannot be made for patients in more advanced disease stages. The most prudent exercise prescription strategy for
people living with HIV to follow is the general ACSM guidelines developed for apparently healthy people[72].

**Design of Exercise Clinical Trials**

Studies in physical activity are commonly designed as one group pre and post test or uncontrolled trials. While these designs are important and valid, they are open to potential bias.[73] These studies may produce positive results in research projects, but not be able to deliver them in the real world due to bias hidden in the study especially in the case of exercise programs.[72] An alternative study design to minimize bias inherent in the aforementioned studies is the randomized clinical trial (RCT). This design is deemed to be the gold standard or highest form of evidence that can be supplied and has become increasingly important as the growth of evidence-based medicine requires a rating of the strength of medical research.[74] While RCTs provide the standard of proof for the evaluation of disease prevention and control interventions, [75] it is important to note that even this type of trial is susceptible to design, execution, and analysis flaws which may bias the results of the study.[74]

The RCT itself is a relatively simple design. The first requirement of this design is that two or more groups are formed through random allocation. Subsequently, one or more of these groups is subjected to an intervention, in this case exercise, and the other serves as a control group. The effectiveness of the exercise intervention can then be assessed by comparing these two groups. This method is particularly beneficial in health care research in that it can deal with the level of complexity that is associated with research in this area and can effectively tease out treatment effects.[72, 74, 75] A critical aspect of the RCT design is the use of a control group. Pre and post-test designs which
only use one group in which an intervention is applied have several inherent problems. Differences seen throughout the course of the study are ascribed to the intervention and a causal connection is then inferred. The first problem with this design is that of temporal trends. Depending on the outcome measures used in the study, some variables may simply change over the course of time regardless of interventions applied. As a result, researchers cannot irrefutably say the changes in their variables were due to intervention alone.[74, 76] In fact, the pre and post-test design has been shown to over-estimate effectiveness of treatments by an average of 61% when compared to studies conducted with a control group. Therefore, the RCT is superior to the pre and post-test design as it has the ability to control for temporal effects on variables through the use of a control group.[74]

Another critical feature of the RCT which adds to the strength of this design is the process of randomly forming the groups for comparison. The main reason for using randomization is to minimize the threat of selection bias, or an incorrect estimate of the effect due to advance knowledge of treatment assignment prior to participant enrollment decisions.[75] The argument can be made that selection bias can be statistically controlled for through the use of multiple regression. However, this can only be accomplished with variables anticipated to have an affect on the outcome. There may be potential confounding variables which will not be measured or anticipated by researchers. This possible error is taken care of when using randomization techniques to form groups.[77] A common technique employed in research is alternation. This is actually considered quasi-randomisation in that it is predictable. Participants are recruited and assigned a group as they enter a clinic alternately giving researchers the ability to alter
the patient schedule leading to a biased allocation. Another similar method is quasi-alternation in which participants are assigned to a group based on criteria such as their month of year of birth or alphabetically by last name. This type of selection can cause a myriad of problems including unequal group numbers and predisposing groups to share common characteristics. Full randomization is preferable to alternation because most statistical tests are based upon mathematic theories of randomness.[78]

True randomization is important to the strength of the study as selection bias is the main threat to internal validity. With random allocation, on average, groups will have the same known and unknown characteristics that could affect outcome. Subsequently, the effect of confounders will be cancelled out in the analysis of the data. The most robust technique is simple randomization. When utilizing this technique a random number list is produced through use of a random number table or statistical software. Participants are then assigned to numbers on the list and researchers may choose whether participants assigned to odd numbers will comprise the control or intervention group. A potential problem when using this method is the fact that unequal groups may be produced, which is a greater concern when dealing with already smaller sample sizes as it can have an affect on the power of the study.[74] Another method that may be used to reduce the chance of imbalanced group sizes is blocked randomization. In addition to controlling size of the groups researchers may also introduce a stratifying variable when it’s important to have equal proportions of this characteristic in each group. Block sizes can vary; however, the smallest size that should be used is four. In a two-armed trial the following allocations would be produced: ABAB, AABB, BABA, BBAA, ABBA, and BAAB. A block of four allocations is then randomly selected from the six possible sets
of blocks, then the next block is selected and so on until there is a long enough string of blocks to allow all the possible participants to be randomized. Using block random allocation will improve power only if the study is rather small.[74] Another way to accomplish stratification on a variable is to use matched randomization. Participants are formed into pairs on the basis of one or more important covariates then randomly assigned to intervention or control which ultimately leads to a balancing of the selected variables.[74] Minimization is an altogether alternative to stratified random allocation in that it prevents numerical and covariate imbalance. This is however a non-random method of forming groups. The first five to ten participants are allocated at random. After the initial randomization, groups are built up through the use of a computer program depending on the characteristics of those already allocated. This process is fairly complex and can lead to technical problems.[71, 76]

Several factors need to be considered when forming groups in a clinical trial. There may be times in which a participant has a strong preference for the treatment and are allocated to the control group which leads to the phenomenon ‘resentful demoralisation’. Participants allocated to the control group who had hoped to receive exercise may seek out alternative treatments, or may not adhere to their “normal” routine which can translate to a dilution bias. One possible way to remedy this problem is to ask for participant preference prior to randomization. The researcher may then randomize indifferent participants and exclude from randomization those who have a strong preference and could therefore bias the trial. The patient preference design requires that a follow-up of the non randomized groups is performed and results are reported with respect to what happens to those who receive the intervention they desire. A draw-back
to this technique is that it may reduce external validity. Another option is to record preference, but utilize a fully randomized technique and evaluate the effect of preference afterwards as a covariate.[74]

Another aspect of the RCT that needs to be addressed is the issue of sample size. It is essential to have an adequate sample size to in order to be confident to say that differences detected have not occurred by chance. Type II errors can occur when a trial is too small, or stating that there is no difference between groups when in actuality there is. The smaller the potential difference, the larger the sample size needed.[79] Historically in health care research trials are too small and therefore underpowered.[71] Many trials do not report a justification for their sample sizes nor any a priori sample size calculations at all.[73] Before calculation of sample size information including study design, hypotheses, mean response and the associated variability of the primary study endpoint, and the desired power at a specified alpha level of significance are required when performing sample size calculation. However, it’s not uncommon to observe discrepancies among study hypotheses, design, statistical analysis, and sample size calculation. These discrepancies can distort the validity and integrity of the trial. Estimation of sample size should be based on an appropriate statistical method or test which is derived under the hypotheses and the study design, for testing the hypotheses in order to achieve a certain degree of statistical inference (80% power) on the effect of the intervention. Appropriate power is needed in order to show statistical significance, but the clinically meaningful difference should be addressed a prior as well. The establishment of a clinically meaningful difference may affect sample size calculation.
The choice may depend up on absolute change, percent change, or effect size of the primary study endpoint.[71]

The exercise intervention itself needs to be highly standardized as crucial components may affect results.[80] For example if the intervention requires the use of an exercise instructor, this person must make sure that they treat each participant or group of participants in the same way to deliver consistency in the treatment. Another critical component of an exercise program is maintenance of the desired training intensity. If exercise is constantly supervised this is performed easily enough, but if participants are asked to complete sessions on their own it must be established that they have to ability to assess their own level of intensity. Another issue which exercise intervention studies encounter is that the control group cannot be treated in exactly the same way as the intervention group. In some studies, the control group is only required to report for pre and post testing, while the exercise group meets several times a week. Prior researchers have attempted to remedy this situation by having the control group meet with the same frequency and duration to simply stretch while the intervention group is performing aerobic exercise. Another factor which comes into play throughout the intervention period is adherence. This issue is complicated by the fact that exercise is freely available to the control group. It would be unethical to deny exercise to study participants, however, there are other ways to remedy this problem such as offering the intervention to the control group once the study is complete. Conversely, participants assigned to the exercise group may not attend all of the exercise sessions. If exploratory dose response analyses are to be included in the study adherence measurements should be recorded.[74]
Lack of blind assessment has also been shown consistently to over-estimate the effect of interventions. Double blind designs are those in which neither the person assessing the participant nor the participant can identify the intervention being assessed. This scenario obviously can not be achieved when exercise is the intervention. It can also be problematic in situations where VO$_{2\text{max}}$ is a primary endpoint. These tests require a great deal of effort on the participant’s part and encouragement is usually provided by research staff throughout the test. This becomes a source of bias when the assessor knows which participants were assigned to the exercise intervention, and may consciously or unconsciously encourage those participants to a higher degree. In this situation it is possible to have a single blind assessor which can reduce bias by controlling for variable assessment and knowledge of group allocation.[74]

The final stage of the RCT that needs to be adequately planned in order to reduce bias at the analysis phase. Using an inappropriate analytical approach can introduce bias. The most robust analytical method that should be used when analyzing the results of randomized trials is through the use of intention to treat analysis (ITT). Once a participant has been randomized they should remain within their group for analytical purposes even if they ‘cross over’ into the other intervention arm or stop their intervention. This type of analysis can be difficult to achieve as it can only occur when 100% of participants are included in the analysis and there is always some form of attrition. Participants who are completely lost to follow-up after randomization and do not provide any data for the analysis will have to be excluded from the analysis. Though pure ITT is difficult to achieve, the analytical philosophy for every trial should be ITT.[81] Under ITT there are two broad analytical strategies: unadjusted and adjusted
analyses. The unadjusted approach simply compares the means of the groups. The differences in the proportions or means are calculated and a statistical test such as the student’s t-test or chi squared test is applied and confidence intervals are calculated. An adjusted analysis is more complex and typically involves some form of regression.[82]

There are several different statistical models that are commonly utilized in exercise clinical trials. The most popular involve the use of Repeated Measures Analysis of Variance, Analysis of Covariance, and T-tests. The statistical model should be determined a priori, in part to avoid the temptation of “data mining”. The statistical model should be relatively simple to carry out if the clinical trial has been well designed.

Researchers commonly evaluate baseline characteristics and pre measures prior to subsequent analysis to assess that the groups are approximately equivalent to each other on various variables. Many statisticians do not recommend this as long as randomization of the groups was carried out properly. In this case differences in baseline characteristics between groups would be attributable to chance and confirming this through statistical analysis does not necessarily aid the analysis, in fact it may mislead researchers. There will inevitably be some statistically significant differences between groups. Differences between groups are more important for smaller trials as there is a greater risk of a chance imbalance among a powerful predictor variable which may change the estimate of the intervention effect.[76] If imbalances are present between groups then steps can be taken to statistically control for potential confounding variables based on the anticipated effect on outcome variables. Baseline comparisons are typically carried out by the use of independent t-tests for continuous variables and chi squared or fisher’s exact tests for non-continuous variables.[83] However, it has also been suggested to assess similarity
between groups by evaluating the amount of effect the variables will have on outcome and the magnitude of the imbalance as opposed to using hypothesis tests.[84]

Repeated Measures ANOVA would seem appropriate for the analysis of an exercise clinical trial in that you measure the same dependent variable more than once in this design. This model has several advantages in that it provides the experimenter the opportunity to control for individual differences among participants, variation from individual differences can be identified and separated from the error term which increases power, and they allow the study of a phenomenon across time. One assumption that must be met for repeated measures ANOVA to be a viable choice is that of sphericity, meaning that when transformed by a set of orthonormal weights, the data are uncorrelated with each other and have equal variances. If the data have a between-subjects factor, the pooled data across all participants must exhibit sphericity which is best estimated by the epsilon statistic. Failure to meet this assumption results in an increase in type I error.[83, 84] Repeated Measures ANOVA can also be misinterpreted in this type of study because the linear model is not entirely correct. The equation used in the calculation of repeated measures ANOVA is based on an assumption that all measurements are made after imposition of the treatment intervention. Since pretest scores are collected prior to the exposure of a treatment or intervention it is impossible for the treatment to affect any of the pretest scores. Considering the intervention affects only the post-test the F tests produced from repeated measures analysis will be biased in the estimation of the treatment effect. If Repeated Measures ANOVA is used the more unbiased interpretation of the data would be drawn from the F-tests of the interaction effect of treatment by time as this will always be the same as the F-test from an analysis of difference scores.[83, 84]
While this method offers a more accurate interpretation, in many cases the results are frequently reported in a way that makes it difficult to determine the adequacy of the analysis.[83, 84] Therefore, authors have recommended in study designs where there is simply a pre-test and one post-test measure Repeated Measures ANOVA is not the most appropriate choice.[85]

An alternative to the repeated measures ANOVA is the use of analysis of covariance (ANCOVA). Analysis of covariance is a combination of regression and ANOVA and assesses whether the treatment effects are different between groups when applied to individuals with the same baseline pretest score while ANOVA tests the hypothesis that the mean posttest scores among treatment groups are equal.[76] In ANCOVA the dependent variable is adjusted for a distracter variable or covariate. In this case the covariate is the baseline measure. A correlation is calculated between the covariate and dependent variable with the end result of a prediction equation used to calculate the predicted dependent variable. The difference between the actual and predicted dependent variable scores is termed the residual. A simple ANOVA is then calculated using each participant’s residual score as the dependent variable. Assumptions for the use of ANCOVA include: 1) errors are independent and normally distributed with mean 0 and common constant variance, 2) population within-groups regression coefficients are equal, 3) the pretest scores are measured without error. Analysis of covariance is relatively robust to deviations from assumption of normality and homogeneity of variance.[85]

ANCOVA is preferable over repeated measures as it can adjust for distracter variables other than the baseline measures and can also increase the power of the F test.
by reducing the size of the error term and reduction in bias as it adjusts for pretreatment differences. The error term is smaller when using ANCOVA due to the fact that within-group variability will be accounted for and removed by the regression of the dependent variable on the covariate. With increased power ANCOVA has the possibility of producing more significant results over ANOVA.[86] There are times in which the use of the baseline to adjust final measurements can result in misleading interpretations. For instance, if the correlations between the covariate and the dependent variable are not equal across the treatment groups, standard ANCOVA is inappropriate.[85]

If ANCOVA is the statistical test to be used, the decision needs to be made as to whether to perform univariate tests for each dependent variable, or to conduct a multivariate test. When using a separate ANCOVA for each dependent variable the probability of making a type I error for each separate test is alpha. However, the probability that one or more of the ANCOVA F tests in the set of F values will result in a type I error does not remain at alpha. If the primary goal is to retain the family error rate at alpha, then univariate procedures would not be appropriate. However, univariate analyses may be undertaken and the alpha level could be adjusted using the Bonferroni technique, in which the alpha level for each dependent variable is adjusted so the sum would equal the desired family error rate. Bonferroni’s test is recommended only when there are a small number of comparisons as the type II error increases causing the power to become low. Conversely, multiple analysis of covariance (MANCOVA) could be used to control the family error rate. Multiple Analysis of covariance utilizes the relationships among the dependent variables and uses an overall test on treatment differences. If the overall F test is significant, then a univariate test on each dependent variable is employed.
Since the selection of dependent variables are carried out a priori and have been selected based on logical analysis there is probably little to be gained by using a complex multivariate technique. The research question should be more focused on which dependent variables are affected by the treatment, which the Bonferonni procedure addresses. The MANCOVA answers the question are treatment effects significant on an optimum linear combination for the dependent variables. MANCOVA may also have very low power if the sample size is small.
REFERENCES


APPENDIX A

INFORMED CONSENT FORM

I. Investigators

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Iris F. Kimura, PhD, ATC, PT; Christopher Stickley, PhD, ATC, CSCS; Ronald K. Hetzler, PhD, FACSM. Kinesiology and Rehabilitation Department. University of Hawaii at Manoa. 1337 Lower Campus Rd, Honolulu Hawaii 96822. Phone: (808) 956-9455

II. Effectiveness of an Exercise Intervention for HIV-infected Patients: A Group-Based Aerobic Protocol

III. Informed Consent

I am being asked to take part in the research study named above because I am infected with HIV, am between 18 and 65 years old, and do not participate in regular exercise.

Before I decide whether or not to take part in this study, I must understand the purpose, how it may help me, any risks to me, and what I have to do. This process is called informed consent. The consent form gives me information about the study that will be discussed with me. Once I understand the study, and if I agree to take part, I will be asked to sign this consent form. I will be given a copy to keep.

Before I learn about the study, it is important that I know the following:

- Taking part is of my own free will.
- I may decide not to take part in the study or stop being in the study at any time without it making any difference to my care now or in the future, or to any benefits that I am allowed.

IV. Expected Length of Time in Study

I will be one of 40 individuals who will participate in this study. I may be enrolled in this study for up to 7 months.
V. Purpose of the Study
The main purpose of this study is to see if a group-based aerobic exercise program can improve health factors related to cardiovascular disease in HIV-infected individuals.

VI. Medication
There are no medications given in this study but there are intensive tests and procedures.

VII. Procedures
If I agree and I qualify for the study, I will participate in an exercise program. The following is a description of what I will be asked to do.

Study Intervention
I will complete an aerobic exercise program at Ala Moana Beach Park three times per week for 3 months in groups of 2-10 people. Each exercise session will consist of: a warm-up lasting ten minutes; continuous aerobic exercise for 20 - 40 minutes; and end with five minutes of stretching. Based on my initial fitness level, I will primarily walk, jog, or run. I will wear a strap around my chest for all exercise sessions to monitor my heart rate. All sessions will be led by two certified athletic trainers. After my 3 month study visits I will have the option to continue with the exercise program for an additional 3 months.

Procedures for the exercise group
I will be asked to come to the Hawaii Center for Aids for study visits at entry and 3 months. I will complete a study visit at 6 months if I decide to participate in the exercise program for an additional 3 months. Because the tests and procedures for this study are complex and some are done at a different location than our clinic, it will take more than one trip to complete visits.

At the visits I will be asked about some general information about myself as well as detailed information about any medical problems I have had in the past and the
medications I have been taking since the last visit. I will be asked to undergo a physical examination and have an EKG (monitors the heart rhythm).

At the entry, 3 month, and at the optional 6 month visit, I will be asked to undergo the following tests and procedures:

**Urine Collection** At each visit, a urine specimen will be taken for routine urinalysis tests. In addition, as drug use may affect neurological testing (see below), my urine will be tested for recent use of drugs. This test will see if I have used the following drugs recently: cocaine and methamphetamines (such as “crystal”, “ice”, “meth”).

**Blood Draw** I will be asked to come fasting (nothing except water for 12 hours before the blood draw) and about 5-6 tablespoons of blood will be drawn. This blood will be sent for complete blood count (CBC), chemistries including glucose, insulin and lipids (cholesterol and triglyceride), and HIV specific tests such as CD4 (type of white blood cell that fights infection) and viral load (amount of HIV in the blood). Blood will also be stored and may be tested later for future studies. I will be asked to sign a separate blood storage consent form.

**Questionnaires** I will be asked to fill out questionnaires about my medical history, eating habits, attitudes towards exercise, fatigue level and quality of life. These should take about 35 minutes to complete.

**A whole body dual energy absorptiometry (DXA)** This measures whole body fat and lean tissue density by a dual-energy x-ray absorptiometry (DXA) scan. A DXA scan is a special kind of x-ray using a small amount of radiation, allowing the doctor to see parts of the body better than a regular x-ray. During the DXA scan, I will need to lie very still on a table for about 10 minutes. The machine will then take the x-rays. This scan takes about 15 minutes and will be done in the clinic.

**A Maximal Exercise Test**
I will complete a maximal graded exercise test on a stationary bicycle. For this test, I will wear headgear with a mouth-piece so researchers can measure the amount of oxygen I’m using. For the test, I will pedal at a pace that I select and the resistance will increase each minute until I feel like I can no longer pedal. During the test, investigators will monitor me with an electrocardiogram (EKG) and a heart rate monitor, take my blood pressure and ask me about how I’m are feeling. After the test is over, I will cool down for at least five minutes. After the exercise test a small amount of blood will be collected from me by finger prick. This test takes about 30 minutes and will be done in the clinic.

At entry and at 3 or 6 mos. (6 mos. if I decide to extend the exercise program) I will be asked to undergo the following procedures:

**Neuro Evaluation** I will be asked questions about my medical history that affect memory and thinking. A specific evaluation called the Unified Parkinson’s Disease Rating Scale (UPDRS) will be administered by a nurse or study investigator. This test requires me to do certain motor tasks like turning my hands back and forth quickly and repeating certain words. This evaluation will be video imaged so a neurologist (brain specialist) can rate my response. Video imaging will involve close ups of my face, hand, and leg motions as well as my whole body as I am performing specific tasks. This will take about 15-20 minutes. I will be asked to undergo testing of my memory and mental function (neuropsychological testing), which may take 45-60 minutes. I will be asked to not use any recreational (illegal) drugs for one week before this test because it can affect how I do on the test. These tests will be done at the clinic.

**MRI neuroimaging / diffusion tensor imaging (DTI)** I will be asked to go to InVision Imaging Center for my MRI (a test that makes body pictures using magnetic rather than x-ray energy) imaging study. I will be asked to lie very still in a large machine. There is a loud “knocking” noise that the machine makes. This is normal. They will image my brain. The scanning will take approximately 45-55 minutes.

At the conclusion of the exercise program (3 months or 6 months if I choose to continue) I will also be asked to complete the following:

**Questionnaires** Two additional questionnaires about the exercise program which will take about 5 – 8 minutes to complete.
Other Information:

Results of routine tests (CBC, chemistries, CD4 count, viral load, glucose levels, and lipid profile) will be forwarded to my primary care doctor so that they may be used for my medical care. Results of my whole body DXA scan will also be given to my doctor, although this is being done for research and not for medical care.

No clinical standards are available for how to evaluate DTI. This test is being done for research only and the results will not be routinely sent to your doctor. However, I may discuss the results with the study doctors if I am interested in my results.

I may decide to quit the study at any time and it will not make a difference in the care I receive.

I can also be taken off the study without my consent for any of the following reasons:

- The study doctors decide that continuing in the study would be harmful to me;
- I am unable to keep my study appointment;
- Other administrative reasons

VIII. Risks

Risks of Blood Draw: Taking blood may cause some soreness, bleeding or bruising where the needle enters the body, and in a few cases fainting or infection may result.

Risks of EKG: There are no risks linked with this procedure. It is a painless test.

Risks of DXA Scan: The DXA scan is painless and gives off a small amount of radiation. The amount of radiation received during each DXA scan is 1/10\textsuperscript{th} of a chest x-ray and considered safe.

If I have had a lot of x-rays recently, I should discuss this with the study doctor or nurse.

Risks of MRI: The only known risks linked with the neuro-imaging scans are a feeling of anxiety, claustrophobia (feeling enclosed), and potential danger linked with the magnet of the MR machine. I will not be able to participate in this study if I have metal objects in
my body (such as from surgery) that would be dangerous if the magnet caused these objects to move. I will be screened before the test to see if I have metal objects in my body. I will be asked to leave as many metallic objects as possible at home, and I will be asked to remove all metallic objects including jewelry, dentures, glasses, watches, and artificial limbs before the MRI. Injury may also happen if I have a device or metal particles in my body located near a sensitive organ that may be affected by the magnet. Examples of this would include a pacemaker device in the heart, aneurysm clips, or metal pieces from work exposure (metal workers, grinders, shrapnel) in the eyes. For my safety, before the scan is performed, I will be asked questions about my risk of having these pieces of metal in my body.

I must tell the technicians and study staff of any situations described above that may put me at risk.

While the MRI scanner makes a “knocking” noise, I might feel a tingling sensation in my arms or legs. This tingling doesn’t happen often. The noise made by the machine can be very loud and I will be given earplugs to prevent damage to my hearing. The radio waves used in the MRI machine have given burns in about one in a million tests (most of those minor).

People with back problems may feel some pain and soreness from lying on their back during the scan. I will be made as comfortable as possible with pillows. People who are claustrophobic (afraid of being in a closed space) may feel anxious about lying down in the machine for the time of the test. If I am claustrophobic and don’t feel I could complete the test without a mild sedative, I may not be able to complete the study and should inform the doctor or technician.

Risks from maximal exercise testing and exercise: There exists the possibility of certain changes occurring during the exercise test. These include abnormal blood pressure, fainting, irregular, fast or slow heart rhythm, and in rare instances, heart attack, stroke, or death. Muscle soreness may be experienced after exercise.

Risks from physical exam, neuropsychological tests, and medical interview are very small. They can cause anxiety or concern and because some personal questions are asked some people may feel embarrassed. Some of the neuropsychological tests can also be
frustrating. I will not have to answer any questions or complete any tests that make me feel uncomfortable.

While every effort will be made to keep my study records confidential, participating in the study may mean a loss of privacy. All information in this study is private, including the urine drug screen. The information that is gathered will not be given to anyone, including my doctor, without my written permission, within the limits of the law.

IX. Benefits
I may not receive direct/immediate benefits. It is possible that I may get some cardiovascular benefit from the aerobic exercise program. Results of this study may help doctors and other health care professionals make treatment decisions about using exercise as a preventive or therapeutic therapy for HIV-infected individuals.

X. Compensation
To compensate me for my time and travel, I will receive the following:

- $20 for the maximal exercise test
- $40 for the MRI

XI. Safeguards
I will have access to a Hawaii Center for AIDS research doctor familiar with this study if I have questions. During regular hours, I can call (808)-737-2751; after regular office hours, I can call (808) 566-5036 and have a study doctor on call paged for me in case of an emergency.

If my doctors feel that participating in this study would be harmful to me, I will not be enrolled into the study.

XII. Confidentiality
All study information will be confidential (private) to the extent permitted by state and federal law and will not be given to anyone without my written consent (permission). I also understand that I will not be identified (known) in any reports coming from these studies.
A code, which will be known only to study personnel and myself, will be used instead of my name on medical records and the videotapes used in this study. The code will be stored in a locked file cabinet. All medical information about me that identifies me by my name will be stored in a locked file cabinet. Personal information or information about my test results will not be given to anyone without my written permission and my medical records will not be open to anyone except for the University of Hawaii and federal regulatory bodies responsible for oversight of this project. This includes: the Institutional Review Committee of the University of Hawaii (Committee on Human Studies). In addition, InVision will be given my name and contact information, but will not have access to my medical records. My privacy will be respected by these people.

The video images will be destroyed after the results of this study are published or 2 years after the study is done, whichever is first.

XIII. Financial Risks/Non-Compensation for Research-Related Injuries

I understand that if I am injured in the course of this study, I alone may be responsible for the costs of treating my injuries. If I am injured (hurt) as a result of being in this study, the Hawaii Center for AIDS will give me immediate treatment needed for my injuries. The cost of this treatment will be charged to my insurance company or to me. If my insurance company will not pay for these costs, they will be my responsibility. The Center has no program to compensate me in the form of money or anything else should I have an injury. I will then be told where I may get other treatment for my injuries. If I have a research-related injury, I should contact Dr. Cecilia Shikuma or one of the other physician-researchers at (808) 737-2751 right away.

My decision whether or not to take part in this study will not make a difference in my care with any of the hospitals or institutions taking part in this study.

XIV. New Findings

At the end of the study, I will be told when study results may be available and how to learn about them.

XV. Voluntary Consent and Certification

I take part in this study of my own free will. I can stop at anytime for any reason and this will not make a difference in the care I receive. My consent does not take away any of
my legal rights in case of negligence or carelessness of anyone working on this project. I verify that I have read the above or that it has been read to me and that my permission is freely given. A copy of this consent form has also been given to me.
CONSENT TO BE A RESEARCH SUBJECT

Title: Effectiveness of an Exercise Intervention for HIV-infected Patients: A Group-Based Aerobic Protocol

XVI. Signatories

I certify that I have read and that I understand the foregoing, that I have been given satisfactory answers to my inquiries concerning project procedures and other matters and that I have been advised that I am free to withdraw my consent and to discontinue participation in the project or activity at any time without prejudice.

I herewith give my consent to participate in this project with the understanding that such consent does not waive any of my legal rights, nor does it release the principal investigator or the institution or any employee or agent thereof from liability for negligence.

1. ___________________ ___________________________ ________________________
   Patient/Subject’s Name (Print)   Signature   Date

2. ___________________ ___________________________ ________________________
   Researcher’s Name (Print)   Signature   Date

I also understand that if I have any question about my treatment, my rights as a volunteer or any other matter relating to this project, I may call Dr. Cecilia Shikuma at (808) 737-2751 or Dr. Iris F. Kimura at (808) 956-3797 and discuss any questions that I might have. If I cannot obtain satisfactory answers to my questions or I have comments or complaints
about my treatment in this study, I may contact: Committee on Human Studies, University of Hawaii, telephone: (808) 956-5007, email uhirb@hawaii.edu.
Title: Effectiveness of an Exercise Intervention for HIV-infected Patients: A Group-Based Aerobic Protocol

Background Information/Procedures:

My doctor or a member of the research staff would like permission to remove and store some body tissue, body fluid and/or blood to do some tests in the future. The HI Center for AIDS (HICFA) would like to keep some of my tissue/body fluid and/or blood that is left over after all of the tests have been done for the study, for future HICFA-approved research. If I agree, my specimen(s) will be kept and may be used in the future to learn more about HIV.

I can withdraw my consent for the study or any part of the study, including having my samples stored for future testing, at any time. Reports about research done with my specimens will not be given to my doctor or to me. These reports will not be put in my health record. The research will not have any effect on my care.

Things to Think About:

The choice to let researchers keep the left over tissue, body fluid, or blood for future research is up to me. No matter what I decide to do, it will not affect my care.

If I decide now that my tissue, body fluid, or blood can be kept for research, I can change my mind at any time. I can let my doctor know to contact the researchers and let them know that I do not want my specimens used for research. Then the specimens will not be stored and used for future research.
The tissue, body fluid, or blood may in the future, be used for genetic research (about diseases that are passed on in families). Even if my specimens are used for this kind of research, the results will not be put in my health records. If genetic research is done, I will be notified and asked to sign another consent. My specimens will be stored and used for research only and will not be sold.

**Benefits:**

There may be no direct benefits to me, however, my tissue, body fluid or blood that are stored may be used for research in the future that may help people infected with HIV in the future.

**Risks:**

There are very few risks to me. The greatest risk is the loss of privacy. The HICFA will protect my records so that my name, address, and phone number will be kept private. All of the samples that are stored will be stored using code numbers only. My name will not be on any sample that is stored.

All information on the main consent form still applies to this consent.
Contraindications to Exercise

**Absolute**

- A recent significant change in the resting ECG suggesting significant ischemia, recent myocardial infarction (within 2 days), or other acute cardiac event
- Unstable angina
- Uncontrolled cardiac disrhythmias causing symptoms or hemodynamic compromise
- Symptomatic severe aortic stenosis
- Uncontrolled symptomatic heart failure
- Acute pulmonary embolus or pulmonary infarction
- Acute myocarditis or pericarditis
- Suspected or known dissecting aneurysm
- Acute systemic infection, accompanied by fever, body aches, or swollen lymph glands

**Relative**

1. Relative contraindications can be superseded if benefits outweigh risks of exercise. In some instances, these individuals can be exercised with caution and/or using low-level end points, especially if they are asymptomatic at rest.

- Left main coronary stenosis
- Moderate stenotic valvular heart disease
- Electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia)
- Severe arterial hypertension (i.e., systolic BP of >200 mm Hg and/or a diastolic BP of >110 mm Hg at rest)
- Tachydysrhythmia or bradydysrhythmia
- Hypertrophic cardiomyopathy and other forms of outflow tract obstruction
- Neuromuscular, musculoskeletal, or rheumatoid disorders that are exacerbated by exercise
- High-degree atrioventricular block
- Ventricular aneurysm
- Uncontrolled metabolic disease (e.g., diabetes, thyrotoxicosis, or myxedema)
- Chronic infectious disease (e.g., mononucleosis, hepatitis, AIDS)
- Mental or physical impairment leading to inability to exercise adequately
APPENDIX C


Indications for Terminating Exercise Testing

Absolute

- Drop in systolic blood pressure of >10 mm Hg from baseline blood pressure despite an increase in workload, when accompanied by other evidence of ischemia
- Moderately severe angina (defined as 3 on a standard scale)
- Increasing nervous system symptoms (e.g., ataxia, dizziness, or near syncope)
- Signs of poor perfusion (cyanosis or pallor)
- Technical difficulties monitoring the ECG or systolic blood pressure
- Subject’s desire to stop
- Sustained ventricular tachycardia
- ST elevation (+1.0 mm) in leads without diagnostic Q-waves (other than V1 or aVR)

Relative

- Drop in systolic blood pressure of >10 mm Hg from baseline blood pressure despite an increase in workload, in the absence of other evidence of ischemia
- ST or QRS changes such as excessive ST depression (>2 mm horizontal or downsloping ST-segment depression) or marked axis shift
- Arrhythmias other than sustained ventricular tachycardia, including multifocal PVCs, triplets of PVCs, supraventricular tachycardia, heart block, or bradyarrhythmias
- Fatigue, shortness of breath, wheezing, leg cramps, or claudication
- Development of bundle-branch block or intraventricular conduction delay that cannot be distinguished from ventricular tachycardia
- Increasing chest pain
- Hypertensive response (systolic BP of >250 mm Hg and/or a diastolic BP of >115 mm Hg).

1. Baseline refers to a measurement obtained immediately before the test and in the same posture as the test is being performed.
APPENDIX D

HEALTH/INJURY HISTORY AND PHYSICAL ACTIVITY READINESS QUESTIONNAIRE

Instructions: Please complete each question to the best of your knowledge/ability. Please ask the investigators if you have any questions.

Part 1. Participant Information
ID: ____________________

Date of Birth:______________ Age (years) __________ Sex: M / F

Ethnicity:______________

Smoker: YES or NO

If yes, how many cigarettes / packs a day are you currently smoking? ________

If yes, how long have you been a smoker? ________________

Part 2. HIV History

Year diagnosed with HIV: ________________

Current Medications:_____________________________________________________

_______________________________________________________________________

Please list all medications you have been on in the past, including year and duration:

_______________________________________________________________________

_______________________________________________________________________

Part 3. Physical Activity Readiness Questionnaire (© Canadian Society for Exercise Physiology)

Instructions: Please circle one response.
1. Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor? YES or NO
2. Do you feel pain in your chest when you do physical activity? YES or NO
3. In the past month, have you had chest pain when you were not doing physical activity? YES or NO
4. Do you lose your balance because of dizziness or do you ever lose consciousness? YES or NO
5. Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity? YES or NO
6. Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition? YES or NO
7. Have you ever been told that you have peripheral vascular disease?
8. Do you know of any other reason why you should not do physical activity? YES or NO

**Part 4. Medical History:** the subsequent sections were obtained following guidelines for exercise testing (American College of Sports Medicine, 2005).

**A. History:** please check the box any condition you currently have or had in the past.

- [ ] Heart Attack
- [ ] Heart Surgery
- [ ] Cardiac Catheterization
- [ ] Coronary Angioplasty (PTCA)
- [ ] Pacemaker/implantable cardiac
defibrillator/rhythm disturbance
- [ ] Heart valve disease
- [ ] Heart failure
- [ ] Heart transplantation
- [ ] Congenital heart disease
- [ ] Diabetes
- [ ] Asthma
- [ ] Lung Disease
- [ ] Heart murmur
- [ ] Seizures
- [ ] Head injury or concussion
□ Loss of consciousness or memory

B. Symptoms: please check the box for any symptoms you have or had experienced at rest, during or following exercise.

□ Chest discomfort
□ Cough or wheezing
□ Dizziness, fainting, or blackouts
□ Difficulty breathing
□ Abnormal heart beats

Musculoskeletal Symptoms: please check the box for any symptoms you have or had experienced, locate and label the occurrence of each symptom on the figure below.

□ Numbness
□ Tingling
□ Pain
□ Swelling
□ Burning
□ Cramping

Cardiovascular Health: please check the box for any conditions applicable to you.

□ Male over age 45 years
☐ Female over age 55 years
☐ Smoke or smoking cessation within the previous 6 months
☐ High blood pressure (greater than 140/90 mm Hg)
☐ Currently taking blood pressure medication
☐ High cholesterol (greater than 200 mg/dL)
☐ Family history of heart attack or heart surgery before age 55 (father or brother) or age 65 (mother or sister)
☐ Physically inactive (less than 30 minutes of physical activity at least 3 days per week).
☐ Overweight

Explain all “Yes” answers here and any checked boxes:
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

Signature of Physician: ___________________________   Date: ________________

1. **Call 911 and provide initial treatment**
   - First Aid/CPR/AED

2. **Instruct emergency medical services personnel:**
   - To report to Leahi Hospital (3675 Kilauea Ave.)
   - To meet a member of the study staff at the corner of Kilauea and Makapuu avenues
   - That we have an injured patient in need of emergency medical treatment

3. **Provide necessary information to EMS personnel:**
   - Name, address, telephone number of caller
   - Number and condition of victims
   - First-aid treatment initiated
   - Specific directions needed to locate scene

4. **On arrival of EMS personnel, assist with care as needed and provide pertinent information:**
   - Method of injury
   - Condition of victim/vital signs
   - Treatment rendered
1. **Call 911 and provide initial treatment**
   - Locate nearest lifeguard
   - First Aid/CPR/AED

2. **Instruct emergency medical services personnel:**
   - To report to Ala Moana Beach Park, 1585 Kapiolani Blvd
   - To meet a member of the study staff at the entrance closest to the patient
   - That there is an injured patient in need of emergency medical treatment

3. **Provide necessary information to EMS personnel:**
   - Name, address, telephone number of caller
   - Number and condition of victims
   - First-aid treatment initiated
   - Specific directions needed to locate scene

4. **On arrival of EMS personnel, assist with care as needed and provide pertinent information:**
   - Method of injury
   - Condition of victim/vital signs
   - Treatment rendered
APPENDIX G

Screening Sheet for Exercise Study

Are you HIV+? ____________ (If no, excluded)

Are you between 18 and 65 years old? _______ (If no, excluded)

Have you been on the same HAART regimen for the past 6 months? ____ (If no, excluded)

Has your doctor ever told you that you should not participate in exercise? (If yes, excluded)

Do you have any metallic implants in your body that would prevent getting an MRI? (If yes, excluded) ______

Do you have extreme claustrophobia that would prevent getting an MRI? (If yes, excluded) ______

Are you pregnant or is there a possibility of getting pregnant? _____________ (If pregnant, excluded)

Have you ever been diagnosed with a neurological disorder?_________
   If yes, please describe ________________________________________
   ________________________________________

Have you been exercising regularly for the past 3 months? ______
   If yes, what types of activities? ___________________
   How many days per week? ______________________
   How long is each session (mins, hrs?) _____________

Does your job require physical activity? __________
   If yes, what types (walking, lifting?) _____________
   How many days per week? ______________________
   How long is each session (mins, hrs?) ______________

What is your work schedule? _______________________
   When would you prefer to work out? __________________

What other studies are you currently on? ______________________
Inclusion criteria:

YES

___ HIV-infected
___ Age 18-65 yrs
___ Stable HAART regimen defined as no change in medications six months prior to the initiation of the study
___ No regular aerobic conditioning defined as performing less than or equal to 30 minutes of moderate physical activity 2 days a week for 3 months prior to initiation of the study

Exclusion criteria:

NO

___ Metallic Implants
___ Extreme Claustrophobia
___ Active illicit substance abuse
___ Self report of neurological disease
___ Pregnancy
___ Absolute contraindications to exercise as outlined by the American College of Sports Medicine (Appendix B)
___ Factors, that in the assessment of the evaluating clinician, may preclude the participant’s ability to complete the study procedures

Signature/Title________________________________  Date:  __________________
APPENDIX H

Self-Efficacy for Exercise Scale [30]

The following are situations that might affect your participation in exercise. For each one, use this scale where 0 is not confident and 10 is very confident, to indicate how confident you are right now that you could exercise 3 times a week for 20 minutes each time, in each of these situations. Please circle a number for each situation.

<table>
<thead>
<tr>
<th></th>
<th>Not Confident</th>
<th>Very Confident</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. If the weather was bothering you.</td>
<td>0 1 2 3 4 5 6 7 8</td>
<td>9 10</td>
</tr>
<tr>
<td>2. If you were bored by the program or activity.</td>
<td>0 1 2 3 4 5 6 7 8</td>
<td>9 10</td>
</tr>
<tr>
<td>3. If you felt pain when exercising.</td>
<td>0 1 2 3 4 5 6 7 8</td>
<td>9 10</td>
</tr>
<tr>
<td>4. If you had to exercise alone.</td>
<td>0 1 2 3 4 5 6 7 8</td>
<td>9 10</td>
</tr>
<tr>
<td>5. If you did not enjoy it.</td>
<td>0 1 2 3 4 5 6 7 8</td>
<td>9 10</td>
</tr>
<tr>
<td>6. If you were too busy with other activities.</td>
<td>0 1 2 3 4 5 6 7 8</td>
<td>9 10</td>
</tr>
<tr>
<td>7. If you felt tired.</td>
<td>0 1 2 3 4 5 6 7 8</td>
<td>9 10</td>
</tr>
<tr>
<td>8. If you felt stressed.</td>
<td>0 1 2 3 4 5 6 7 8</td>
<td>9 10</td>
</tr>
<tr>
<td>9. If you felt depressed.</td>
<td>0 1 2 3 4 5 6 7 8</td>
<td>9 10</td>
</tr>
</tbody>
</table>
### APPENDIX I

**Maximal Exercise Testing**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting HR</td>
<td></td>
</tr>
<tr>
<td>Resting BP</td>
<td></td>
</tr>
<tr>
<td>Max HR (207 - 0.7*age)</td>
<td></td>
</tr>
<tr>
<td>FiO2 (Pre and Post)</td>
<td></td>
</tr>
<tr>
<td>FiCO2 (Pre and Post)</td>
<td></td>
</tr>
<tr>
<td>Lactate (Pre and Post)</td>
<td></td>
</tr>
<tr>
<td>Self-Selected RPM</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>HR EKG</th>
<th>HR Polar</th>
<th>BP</th>
<th>RPE/Legs</th>
<th>RPE/C/B</th>
<th>RPE/Overall</th>
<th>V02</th>
<th>RES</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>4</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>8</td>
<td></td>
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<td></td>
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<tr>
<td>10</td>
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<td>12</td>
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<td></td>
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<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Test End Time:**

82
APPENDIX J

The Medical Outcomes Study HIV Health Survey (MOS-HIV)[29]

1. In general, would you say your health is: (Check One)

   Excellent .................................................. 1□
   Very Good .................................................. 2□
   Good ......................................................... 3□
   Fair ........................................................... 4□
   Poor ............................................................ 5□

2. How much bodily pain have you generally had during the past 4 weeks? (Check One)

   None .......................................................... 1□
   Very Mild ................................................... 2□
   Mild .......................................................... 3□
   Moderate .................................................... 4□
   Severe ......................................................... 5□
   Very Severe .................................................. 6□

3. During the past 4 weeks, how much did pain interfere with your normal work (or your normal activities, including work outside the home and housework)? (Check One)

   Not at all ...................................................... 1□
   A little bit .................................................... 2□
4. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

<table>
<thead>
<tr>
<th>(Check <strong>one</strong> box on each line)</th>
<th><strong>YES,</strong> limited a lot</th>
<th><strong>YES,</strong> limited a little</th>
<th><strong>NO,</strong> not limited</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. The kinds or amounts of vigorous activities you can do, like lifting heavy objects, running or participating in strenuous sports.</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
</tr>
<tr>
<td>b. The kinds or amounts of moderate activities you can do, like moving a table, carrying groceries or bowling.</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
</tr>
<tr>
<td>c. Walking uphill or climbing (a few flights of stairs).</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
</tr>
<tr>
<td>d. Bending, lifting or stopping.</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
</tr>
<tr>
<td>e. Walking one block.</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
</tr>
<tr>
<td>f. Eating, dressing, bathing or using the toilet</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
</tr>
</tbody>
</table>
5. Does your health keep you from working at a job, doing work around the house or going to school?

(Check One)

Yes………………………………………………………… 1 □

No…………………………………………………………. 2 □

Have you been unable to do certain kinds of amounts of work, housework, or schoolwork because of your health?

(Check One)

Yes…………………………………………………………. 1 □

No ……………………………………………………………. 2 □
For each of the following questions, please check the box for the one answer that comes closest to the way you have been feeling during the past 4 weeks.

6. How much of the time during the past 4 weeks, has your health limited your social activities (like visiting with friends or close relatives?)

<table>
<thead>
<tr>
<th>All of the Time</th>
<th>Most of the Time</th>
<th>A Good Bit of the Time</th>
<th>Some of the Time</th>
<th>A Little of the Time</th>
<th>None of the Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
<td>4 □</td>
<td>5 □</td>
<td>6 □</td>
</tr>
</tbody>
</table>

7. How much of the time, during the past 4 weeks:

<table>
<thead>
<tr>
<th></th>
<th>All of the Time</th>
<th>Most of the Time</th>
<th>A Good Bit of the Time</th>
<th>Some of the Time</th>
<th>A Little of the Time</th>
<th>None of the Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Have you been a very nervous person?</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
<td>4 □</td>
<td>5 □</td>
<td>6 □</td>
</tr>
<tr>
<td>b. Have you felt calm and peaceful?</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
<td>4 □</td>
<td>5 □</td>
<td>6 □</td>
</tr>
<tr>
<td>c. Have you felt downhearted and blue?</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
<td>4 □</td>
<td>5 □</td>
<td>6 □</td>
</tr>
<tr>
<td>d. Have you been a happy person?</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
<td>4 □</td>
<td>5 □</td>
<td>6 □</td>
</tr>
<tr>
<td>e. Have you felt so down in the dumps that nothing could cheer you up?</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
<td>4 □</td>
<td>5 □</td>
<td>6 □</td>
</tr>
</tbody>
</table>
8. How often during the past four weeks:

<table>
<thead>
<tr>
<th>All of the Time</th>
<th>Most of the Time</th>
<th>A Good Bit of the Time</th>
<th>Some of the Time</th>
<th>A Little of the Time</th>
<th>None of the Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Did you feel full of pep?</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
<td>4 □</td>
<td>5 □</td>
</tr>
<tr>
<td>b. Did you feel worn out?</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
<td>4 □</td>
<td>5 □</td>
</tr>
<tr>
<td>c. Did you feel tired?</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
<td>4 □</td>
<td>5 □</td>
</tr>
<tr>
<td>d. Did you have enough energy to do the things you wanted to do?</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
<td>4 □</td>
<td>5 □</td>
</tr>
<tr>
<td>e. Did you feel weighed down by your health problems?</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
<td>4 □</td>
<td>5 □</td>
</tr>
<tr>
<td>f. Were you discouraged by your health problems?</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
<td>4 □</td>
<td>5 □</td>
</tr>
<tr>
<td>h. Were you afraid because of your health?</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
<td>4 □</td>
<td>5 □</td>
</tr>
</tbody>
</table>

9. How much of the time, during the past 4 weeks:

<table>
<thead>
<tr>
<th>All of the Time</th>
<th>Most of the Time</th>
<th>A Good Bit of the Time</th>
<th>Some of the Time</th>
<th>A Little of the Time</th>
<th>None of the Time</th>
</tr>
</thead>
</table>

87
10. Please check the box that best describes whether each of the following statements is true or false for you.

<table>
<thead>
<tr>
<th></th>
<th>Definitely True</th>
<th>Mostly True</th>
<th>Not Sure</th>
<th>Mostly False</th>
<th>Definitely False</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. I am somewhat ill.</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
<td>4 □</td>
<td>5 □</td>
</tr>
<tr>
<td>b. I am as healthy as anybody I know.</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
<td>4 □</td>
<td>5 □</td>
</tr>
<tr>
<td>c. My health is excellent.</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
<td>4 □</td>
<td>5 □</td>
</tr>
</tbody>
</table>
d. I have been feeling bad lately.

11. How has the quality of your life been during the past 4 weeks? That is, how have things been going for you?

   (Check One)
   
   Very well; could hardly be better
   .......................................................... 1 □
   
   Pretty good
   .......................................................... 2 □
   
   Good and bad parts about equal
   .......................................................... 3 □
   
   Pretty bad
   .......................................................... 4 □
   
   Very bad; could hardly be worse
   .......................................................... 5 □

12. How would you rate your physical health and emotional condition now compared to 4 weeks ago?

   Much better
   .......................................................... 1 □
   
   A little better
   .......................................................... 2 □
   
   About the same
   .......................................................... 3 □
   
   A little worse
   .......................................................... 4 □
   
   Much worse
   .......................................................... 5 □
APPENDIX K

Physical Activity Group Environment Questionnaire [28]

This questionnaire helps you assess your perceptions of an exercise group of which you are a member. There are no right or wrong answers, so please give your immediate reaction. Some of the questions may seem repetitive, but please answer them all and be as honest as possible.

The following questions help assess your feelings about your personal involvement with your exercise group. On a scale of 1 through 9, 1 indicating the strongest agreement, and 9 indicating the strongest disagreement, answer each question.

1. I like the amount of physical activity I get in this program.
   ______

2. This physical activity group provides me with a good opportunity to improve in areas of fitness I consider important.
   ______

3. I am happy with the intensity of the physical activity in this program.
   ______

4. I like the program of physical activities done in this group.
   ______

5. I enjoy new exercises done in this physical activity group.
   ______

6. This physical activity group provides me with good opportunities to improve my personal fitness.
   ______

7. This physical activity group is an important social unit for me.
   ______

8. I enjoy my social interactions within this physical activity group.
   ______

9. I like meeting the people who come to this physical activity group.
   ______
10. If this program was to end, I would miss my contact with the other participants.

11. In terms of the social experiences in my life, this group is very important.

12. The social interactions I have in this physical activity group are important to me.

13. Our group is united in its beliefs about the benefits of the physical activities offered in this program.

14. Our group is in agreement about the program of physical activities that should be offered.

15. Members of our group are satisfied with the intensity of physical activity in this program.

16. Members of our group enjoy helping if work needs to be done to prepare for the activity sessions.

17. We encourage each other in order to get the most out of the program.

18. Members of our physical activity group often socialize during exercise time.

19. Members of our physical activity group would likely spend time together if the program were to end.

20. Members of our group sometimes socialize together outside of activity time.

21. We spend time socializing with each other before and after our activity sessions.
APPENDIX L

Exercise Instructor Questionnaire

Please indicate the level to which you agree or disagree with the following statements about the exercise instructor.

<table>
<thead>
<tr>
<th>The exercise instructor was:</th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Agree</th>
<th>Strongly Agree</th>
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</thead>
<tbody>
<tr>
<td>knowledgeable</td>
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<tr>
<td>clear</td>
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<tr>
<td>enthusiastic</td>
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<tr>
<td>showed interest in participants</td>
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<td>supportive</td>
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<td>appeared fit</td>
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APPENDIX M

Ratings of Perceived Exertion (RPE) Scale Script

(Modified Borg RPE Scale, Borg 1998)

Several times during the test, we will ask you to rate the work, according to the RPE scale. You will be asked to choose a number to describe how hard the work is for you. A rating of “6” would correspond to those feelings and sensations you have during the easiest work you can imagine, similar to sitting in a chair. A rating of “20” corresponds to the feelings and sensations you would have during the most difficult work you could imagine yourself doing, so exhaustive that you cannot continue. Every two minutes, we will ask you to give local muscular ratings for perceived exertion and feelings of strain in the legs and joints; central readings which are sensations involving the chest and breathing; and overall readings, for which you may integrate the local and central sensations in the way you feel appropriate. Please point to the number that you feel is appropriate.

RPE Scale

6

7

Very, very light

8

9

Very light

10

11

Fairly light

12

13

Somewhat hard

14

15

Hard

16

17

Very hard

18

19

Very, very hard

20

93
APPENDIX N

Exercise Session Data Collection Sheet

PID: ____________

<table>
<thead>
<tr>
<th>Date</th>
<th>Target Duration</th>
<th>Target %HRR</th>
<th>Target HR</th>
<th>Actual Duration</th>
<th>Average HR</th>
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