**TITLE:** Strength Training and Endurance Exercise for LIFE

**Trial #** NCT02102060
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**Ethics approval and consent to participate**
The study was approved by the Institutional Review Boards at the Salem VAMC, Salem, VA and the University of Maryland IRB, Baltimore, MD.
Written informed consent was obtained from each patient prior to participation.

## Protocol Overview

**Hypothesis:** We hypothesize that high-intensity exercise training will increase cardiorespiratory fitness, which will be mediated by improved diastolic function and will correlate with decreased biomarkers of inflammation.

**Background:** Adults with HIV on antiretroviral therapy have a life expectancy approaching that of the general population yet have impaired cardiorespiratory fitness and diastolic function that increase their risk for age-related disability. Chronic inflammation is a well-studied mediator of advanced aging with HIV, including cardiac dysfunction, yet the impact of exercise training is unclear. The study objective is to develop an exercise program for older adults with HIV that targets pathophysiological processes of advanced aging and will prevent and improve disability.

**Design**: The study is a randomized trial comparing 16-weeks of progressive aerobic and resistance training to usual care in sedentary older (50+ years) adults with HIV. The center-based exercise training is performed three times weekly under supervision. The end-target duration and intensity of aerobic exercise is 45 minutes at 70-80% of baseline heart rate reserve. Resistance training progresses from low-intensity to high-intensity based on initial one repetition maximum (1-RM) in the three upper body (chest press, seated row, pull-down) and three lower body exercises (leg press, knee extension, knee flexion). Primary outcomes are cardiorespiratory fitness, cardiac function, and biomarkers of myocardial fibrosis and cardiac stress. Secondary outcomes include muscle strength, body composition measured by Dual-energy X-ray absorptiometry (DXA), and biomarkers of systemic Inflammation.

## Statistical Analysis Plan (SAP)

### Power Analyses

Power calculations were based on results from randomized exercise trials that included a sedentary control group. For outcomes of diastolic function[1], cytokines [2], and biomarkers of myocardial fibrosis[3] we used mean (SD) from exercise trials in older adults without HIV since results were not available for adults with HIV. Referenced values for $VO_2$peak[4] and strength[5] were obtained from trials in adults with HIV, but a younger population (mean age 30-45 years old). For these outcomes, a sample size of 22 participants per group provides at least 80% power to detect a between group difference with a two-sided alpha of 0.05. We acknowledge that older participants may have greater muscle soreness or fatigue as well as more medical problems. Therefore, our target enrollment number assumes a conservative attrition rate of 30% based on prior exercise interventions in adults with HIV.[6,7]

### Statistical Analyses

ANOVA will be used to compare the change in the intervention group to the change in the control group for the following primary outcomes, AIM 1: (1) functional performance, (2) aerobic capacity, (3) diastolic function; AIM 2: (1) strength, (2) muscle mass. In the ANOVA models, the change from baseline to 16-weeks will be the dependent variable in models adjusted for the baseline value of the outcome measure and treatment group. Groups will be compared at baseline for differences in potential confounders such as age and comorbidity. Additional adjustment will be made if the randomization produces groups that are not balanced on factors which are also associated with outcomes. We do not anticipate needing to adjust for sex, history of AIDS, or length of HIV infection (CD4 cell count) as our group assignment will be blocked on these factors. Similar analyses will be performed for secondary outcomes, intramuscular fat,

percent body fat, plasma glucose, insulin, and lipids, blood pressure. All analyses will be two-tailed.

We will use regression analyses to test the following associations, Specific aim 1: change (16-week value minus baseline value) in VO2peak with change in (1) diastolic function and (2) markers of systemic chronic inflammation, (3) change in diastolic function with change in myocardial fibrosis; Specific Aim 2 (1) change in strength with change in muscle mass, (2) change in muscle mass with change in markers of inflammation, change in intramuscular fat with change in (3) plasma lipid and (4) fasting glucose concentrations. These analyses will be adjusted as noted above, except they will not be adjusted for group as the analytic interest lies in the relation of change to change, not change to group.

Analyses will include subjects who drop out before completion of the 16-week study period by way of multiple imputation. This intention to treat approach will investigate factors that may affect compliance and difficulty with exercise training, including pain/soreness and medical comorbidity. If the pattern of missing data is missing completely at random, or simply at random, our multiple imputation should eliminate bias due to loss to follow-up. Because the majority of the subjects will be recruited from the Salem VA HIV clinic, we will be able to obtain clinical data from subjects who drop out of the study, but remain in clinical care, to determine if drop-out was related to medical conditions that may influence outcomes. Thus, we will be able to estimate bias introduced by loss to follow-up. If there is sufficient information, we may be able to model the drop-out process and adjust our analyses for loss to follow-up even if the missing data pattern is non-ignorable. If 48 training sessions cannot be completed in 16 weeks, then total training time will be tracked, and incorporated into the data analysis.

**Data management**

A robust data management plan is in place to ensure the accuracy, completeness, legibility, and timeliness of the data collected across the two sites. The study data is managed carefully to ensure its integrity. Ongoing quality assurance activities include summary statistics to identify outliers that are then confirmed with source documents. To maintain participant confidentiality, each participant is assigned a numerical ID which is used on all case report forms, data sheets and surveys. The keycode to link individuals with their assigned IDs are stored in locked cabinets and computer folders separate from study data. Data is entered directly from the source documents into data spreadsheets that are stored in limited access study folders on the VA server that can be accessed only through a password protected VA computer from either site.

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