PROTOCOL: Exercise Training to Improve Brain Health in Older HIV+ Individuals
VERSION: 13 (4/7/2020)
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A Introduction

A1 Study Abstract

Management of older persons living with HIV (PLWH) (≥ 40 years old) is becoming increasingly more complex as a majority is greater than 40 years old. Attempts to improve the quality of life of older PLWH using adjunctive therapeutics to combination antiretroviral therapy (cART) have largely been unsuccessful.

While the impact of physical activity on brain health (assessed by neuropsychological performance and neuroimaging) has been well studied in older healthy HIV uninfected (HIV-) individuals and neurodegenerative conditions, few studies have concentrated on older PLWH. Both clinically and pathophysiologically, HIV associated neurocognitive disorders (HAND) differs from other neurodegenerative disorders seen with aging (e.g. Alzheimer's disease (AD). A positive association relationship between exercise and cognition has been observed in PLWH, but physical activity has been primarily examined using self-report questionnaires that are subjective and not quantitative. To date, no study has focused on the direct effects of exercise on neuropsychological performance or neuroimaging in PLWH.

The objective of this proposal is to conduct a prospective controlled intervention trial to determine if an increase in physical activity through a monitored aerobic and resistance exercise (EXS) program improves brain health in older PLWH. We will quantify physical function (physical activity using cardiorespiratory capacity and actigraphy) and brain function [neuropsychological performance testing and neuroimaging (cerebral blood flow (CBF) and brain volume)] in older physically inactive PLWH at baseline and 26 weeks after randomization to either an EXS or a social-interaction stretching (SIS) program. In addition, we will obtain serum markers of neurogenesis, glucose regulation, and systemic inflammation.

A direct impact of these expected outcomes will be the adoption of a more physically active lifestyle by older PLWH and improved EXS guidelines and programs for older PLWH.

A2 Primary Hypothesis

Specific Aim 1. Examine the effects of exercise on cognitive function in older PLWH.
Specific Aim 2. Examine the effects of exercise on brain structural/functional measures in older PLWH.

Secondary endpoints of this proposal will identify implementation factors needed to scale up an EXS program in older PLWH to HIV clinics at multiple institutions. Key barriers and facilitators will be analyzed from qualitative data obtained from questionnaires, focus groups, and in-depth interviews of shareholders. We will also investigate the effect of exercise on any changes in the stool or intestinal mucosal microbiome/microbiota/metagenome.

A3 Purpose of the Study Protocol

Management and treatment of older persons living with HIV (PLWH) (≥ 40 years old) is becoming increasingly more complex as a majority is greater than 40 years old. This proposal will conduct a prospective controlled intervention trial to assess the quantitative and qualitative effects of a monitored aerobic/resistance exercise (EXS) program compared to a social-interaction stretching (SIS) program on brain health (neuropsychological performance testing and neuroimaging measurements) in older PLWH. These results could influence public health policy by encouraging PLWH to adopt a more physically active lifestyle and stimulate the development of effective EXS programs for older PLWH.

B Background

B1 Prior Literature and Studies

2.1 People living with HIV (PLWH) are aging. The number of older PLWH is increasing due to the efficacy of combination anti-retroviral therapy (cART) [3, 32]. A majority of PLWH in the United States (US) are now greater than 40 years old [33]. These older PLWH are often frail [4, 10, 13, 34-36] and place significant

strains on medical resources [37]. Older PLWH also have higher unemployment rates [38]; are frequently unable to perform activities of daily living; and are a significant burden to their caregivers [39, 40]. Relative to their younger counterparts, older PLWH have a greater than two-fold elevated risk of morbidity [41-43] and are at increased risk for developing HIV associated neurocognitive disorders (HAND) [43]. Recent reports from the NIH Office of AIDS Research and the US Senate Special Committee on Aging [44] emphasize a public health priority to identify research that improves the brain health of this vulnerable and growing population [9].

2.2 HAND remains prevalent despite cART. Even with virologic control, PLWH can develop perturbations in the central nervous system (CNS) including cognitive dysfunction and neuroimaging abnormalities [e.g. reduced volumetrics and cerebral blood flow (CBF)] [3]. The presence of HAND results from non-mutually exclusive factors including irreversible injury prior to initiating cART, persistent HIV in the CNS [1, 45], antiretroviral toxicity [46-48], vascular/metabolic disorders [49], and/or chronic CNS inflammation [3]. While normal aging causes cognitive changes and brain atrophy [50], PLWH may experience accelerated or augmented aging [51].

2.3 Adjunctive therapies for HAND have not been successful. Therapeutic trials have typically concentrated on younger PLWH with more advanced cognitive impairment [52]. These trials used a variety of medications (e.g. memantine, minocycline, selegiline), but had limited success. A Cochrane review found no evidence for improved cognition or quality of life for PLWH [53] due to adjunctive therapies. A critical gap remains as no effective adjunctive therapies to cART exist for improving brain health, especially in older PLWH.

2.4 While multiple commonalities exist between HAND and other neurodegenerative disorders of aging (e.g. Alzheimer's disease (AD)), notable differences exist. The fact that many PLWH are experiencing cognitive and neurological decline during mid- life that resemble the neurological functioning of older HIV(-) individuals suggests that premature cognitive aging can occur despite cART [4, 13, 54] . Yet obvious differences in clinical trajectories and pathophysiology exist between HAND compared to other neurodegenerative conditions of aging (e.g. AD) [7, 8]. HAND is characterized by psychomotor slowing and executive dysfunction with severe dementia rarely observed if the virus is well controlled. In contrast, AD is characterized by progressive cognitive decline, often within certain domains (memory, learning, attention), that results in severe dementia. The correspondence between viral pathogen, immunological disturbance, and cognitive decline that is an essential feature of HAND does not exist for other neurodegenerative disorders.

2.5 A combination of aerobic and resistance exercise (EXS) training (EXS) modulates declines in brain health due to aging and neurodegeneration within HIV(-)individuals. Recent cross-sectional studies and meta-analyses of HIV(-) individuals have noted that baseline physical inactivity, as assessed by actigraphy or oxygen consumption (e.g. VO_2), predicts future cognitive decline [55-62]. A number of studies have compared an EXS program to a social interaction-stretching (SIS) intervention in HIV(-) individuals [59, 63-66]. Overall, HIV(-) individuals who engaged in an EXS program that is at least 26 weeks in duration had significant improvements in cognition compared to those who participated in a SIS program. Improvements in cognition due to an EXS program were typically seen in attention, memory, and executive function domains [67]. An EXS program also improved brain structure and function. HIV(-) individuals who participated in an EXS program had significant increases in brain volume (anterior cingulate and hippocampus) and CBF (anterior cingulate and putamen) compared to individuals in a SIS program [56, 61, 68-70]. To date, most EXS programs have concentrated on certain neurodegenerative disorders (e.g. early onset AD), and not older PLWH. Due to differences in HAND and AD (Sec 2.4), the ability to successfully translate an EXS program to older PLWH remains an important gap that needs to be studied.

2.6 EXS programs that have been developed for PLWH have primarily concentrated on physiological outcomes and <u>not</u> brain health. Our group and others have demonstrated that exercise improves physical function (e.g. cardiorespiratory capacity), systemic inflammatory markers [e.g. D-dimer, interleukin (IL)-6, high sensitivity c-reactive protein (hsCRP)], and glucose regulation [fasting glucose, insulin concentrations, and homeostatic model assessment of insulin resistance (HOMA-IR)] in PLWH [71-78]. However, mixed results have been observed within the few studies that have studied the relationship between exercise and brain health in PLWH. While an early study showed that habitual physical activity had minimal benefit on cognition [79], subsequent studies in PLWH have shown that individuals who engage in exercise exhibit better cognitive performance compared to sedentary individuals [21-25]. Most studies investigating the effects of exercise on brain health have been limited by their cross-sectional design; use of a self-report questionnaire to assess physical activity (often the response to a single question); use of non-objective cognitive performance measures, and their focus on younger physically active PLWH [21-25]. An important gap remains as older sedentary PLWH, who often benefit the most from an EXS program [80], have often been ignored.

2.7 A conceptual model exists for the specific benefits of an EXS program on brain health in older PLWH compared to HIV(-) individuals. This proposal will mechanistically study the effects of EXS on brain health through indirect and direct pathways [81]. We hypothesize that EXS training in older PLWH will primarily affect the indirect pathway by increasing physical fitness (cardiorespiratory capacity and daily physical activity as measured by actigraphy). Observed changes in the indirect pathway will be primarily modulated by decreases in systemic inflammation (hsCRP, IL-6, and D-dimer) [61, 82, 83] and improved glucose regulation [reduced fasting glucose and improved insulin sensitivity (HOMA-IR)]. We hypothesize that EXS training will also affect the direct pathway, but to a lesser extent, with modest upregulation of growth factors [e.g. brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), and insulin like growth factor (IGF)-1] [61, 82, 83]. Observed changes in both the direct and indirect pathways will lead to improvements in brain health in older PLWH that can be quantitatively measured by changes in cognition [improved neuropsychological performance (NP) within certain domains (executive, memory, and attention)] and neuroimaging (increases in brain volumetrics and CBF within cortico-striatal networks). While EXS could reduce HAND by these multiple mechanisms (reduced inflammation, improved glucose regulation, increased neurogenesis), the relative strength of these mechanisms remains unknown and is a focus of this proposal.

2.8 This exploratory trial could guide professional recommendations. Recent treatment guidelines for PLWH suggest a role for physical activity as an adjunctive therapy to cART but specific recommendations are lacking [84]. Currently, few older PLWH receive guidance from their healthcare providers concerning the potential benefits of a physically active lifestyle[85], especially in regards to brain health. This gap may reflect the relative absence of studies that have examined the effects of EXS on brain health in PLWH. This proposal uses a mixed model approach [30] that goes beyond typical observational and cross-sectional comparisons that have been previously used. Quantitative assessments of physical function (cardiorespiratory capacity and actigraphy) and brain function [NP and neuroimaging (volumetrics and CBF)] will be obtained in older sedentary PLWH at baseline and 26 weeks after an EXS or SIS program (2:1 randomization respectively). We will now capture aspects of the implementation process (e.g. program satisfaction, sustainability of behavior change) through interviews with staff and participants at several time points throughout the intervention. In addition, interviews will be conducted with participants to identify key barriers and facilitators for participation in an EXS program. This information, along with measures of modifiable participant engagement factors (e.g. stage of behavior change, self-efficacy, social support) will allow for scale-up to HIV clinics at multiple institutions.

C Study Objectives

C1 Primary Aims

Specific Aim 1. Examine the effects of exercise on cognitive function in older PLWH. Hypothesis 1a: A 26 week EXS program in older sedentary PLWH will enhance specific domain (executive function, attention, and memory) NP compared to a SIS program.

Hypothesis 1b: Greater improvements in physical function (daily physical activity and cardiorespiratory capaci-ty) due to EXS will be associated with better cognitive performance.

Exploratory Hypothesis: Improvements in cognition due to EXS will be accompanied by reduced systemic inflammation and improved glucose regulation.

Specific Aim 2. Examine the effects of exercise on brain structural and functional measures in older PLWH.

Hypothesis 2a: A 26 week EXS program in older sedentary PLWH will improve brain neuroimaging measures (volumetrics and CBF) compared to a SIS program.

Hypothesis 2b: Greater improvements in physical function (daily physical activity and cardiorespiratory capacity) due to EXS will be associated with increases in brain volumetrics and CBF. Hypothesis 2c: Improved neuroimaging changes will be associated with enhanced cognition.

Exploratory Hypothesis: Increases in neuroimaging measures due to EXS will be accompanied by reduced sys-temic inflammation and improved glucose regulation.

C2 Secondary Aim

Secondary endpoints of this proposal will identify implementation factors needed to scale up an EXS program in older PLWH to HIV clinics at multiple institutions. Key barriers and facilitators will be analyzed

from qualitative data obtained from questionnaires, focus groups, and in-depth interviews of shareholders.

C3 Innovation/Rationale for the Selection of Outcome Measures

3. INNOVATION

3.1 A trans-disciplinary team of researchers will examine relationships between EXS and brain health in older PLWH. This explanatory proposal integrates HIV researchers in neurology/radiology (Dr. Ances), neuropsychology (Dr. Paul), endocrinology/metabolism (Drs. Yarasheski and Reeds), physical therapy/medicine (Drs. Yarasheski, Reeds, and Cade), statistics (Dr. Vaida), behavioral science/public health (Dr. Eyler), and geriatric psychiatry (Dr. Lenze). A mixed method model design will allow us to leverage our expertise to gain a greater understanding of the inter-relationships among HIV, exercise, and brain health [30].

3.2 Quantitative physical activity measurements will improve our understanding of the effects of an EXS program on brain health in older PLWH. Prior studies examining the effects of exercise on brain health have typically used subjective measures of physical activity [26]. In contrast, we will obtain objective measures of physiological response to either an EXS or SIS program. These quantitative measures are often difficult to obtain and can be confounded by effort-dependence and "learning effects". Our team (Drs. Yarasheski, Reeds, Cade) has significant experience (>20 years) implementing, monitoring, and interpreting physiological responses to exercise interventions in older adults, especially PLWH [86-90]. We will objectively monitor the "dose", type, frequency, intensity, and duration of each exercise session and quantify the respective physiological adaptations. Self-efficacy, enjoyment, and social support will now be assessed (Dr. Eyler) to identify crucial factors needed for encouraging long-term participation in an EXS program.

3.3 The combination of aerobic and resistance exercise will provide greater benefit for brain health than either intervention alone in older PLWH. Our EXS program adheres to established guidelines by the American College of Sports Medicine (ACSM) [91]. The program has been developed by a licensed physical therapist (Dr. Cade) and exercise physiologist (Dr. Yarasheski) and will be supervised by a certified trainer. Our group has successfully implemented a similar EXS program in a separate PLWH cohort, but we did not focus on brain health [77]. It is important to combine aerobic and resistance training because both muscle weakness and poor endurance are common in older PLWH and often limit their ability to engage in physical activities [75, 76, 92]. Aerobic training will improve exercise tolerance and cardiovascular health by increasing cardiac, skeletal, and cerebral blood flow and oxygen extraction [93] . The addition of resistance exercise training will improve glucose regulation and the plasma lipid profile [94, 95]. Our proposal is the first to quantitatively study the effects of a combination of aerobic and resistance exercise on brain health outcomes in older PLWH.

3.4 Novel neuroimaging methods will provide a greater mechanistic grasp of the effects of exercise on brain health in older PLWH. Dr. Ances has significant expertise in utilizing novel neuroimaging techniques to study PLWH [96-99]. Arterial spin-labeling (ASL), which exploits labeled arterial blood water as an endogenous diffusible tracer, will be used to non-invasively measure CBF [96, 100, 101]. ASL has several advantages compared to other neuroimaging methods[97] including: 1) it can be repeatedly performed as it uses arterial blood water as an endogenous tracer. This method avoids the need for injection of expensive and potentially harmful radioisotopes; 2) it provides quantitative resting CBF values in mL/100gm/min without arterial blood sampling; 3) it can be acquired in the same session as structural magnetic resonance imaging (MRI); 4) it has excellent reproducibility and provides stable measurements of CBF across different scanning sessions; and 5) it can be performed in less than 10 minutes and is available on most clinical scanners [102, 103]. Our protocol is similar to the AIDS Clinical Trial Group (ACTG) (Dr. Ances- neuroimaging PI for A5310 and A5324) and Alzheimer's Disease Neuroimaging (ADNI) and will allow us to directly compare results from older PHWH with other HIV(-) cohorts.

3.5 Acquisition of qualitative measures throughout the intervention will allow us to identify key barriers and facilitators for translating an EXS program to HIV clinics at multiple sites. While this explanatory proposal studies the effects of EXS on brain health in PLWH, we believe that this study will also accelerate the translation of findings into clinical practice. In order to gain a sound understanding of contextual factors that affect implementation of an EXS program for older sedentary PLWH, we will conduct interviews and focus groups with staff and participants at several time periods during the intervention (Dr. Eyler). This will allow us to 1) tailor aspects of the program to coincide with reported barriers to implementation (e.g. through staff interview); 2) develop strategies to enhance adherence; and 3) make recommendations for future intervention strategies based on modifiable psychosocial characteristics of PLWH as they progress through the intervention. With the assistance of a geriatric clinical trialist (Dr. Lenze), our goal is to synthesize research findings and translate them into clinical practice, in terms of recommendations for older PLWH (Levin letter) and improved EXS guidelines for clinicians (Dr. Yarasheski letter).[104]

D Study Design

D1 Overview or Design Summary

The objective of this proposal is to conduct a prospective controlled intervention trial to determine if an increase in physical activity through a monitored **aerobic and resistance exercise (EXS)** program improves brain health in older PLWH. We will quantify physical function (physical activity using cardiorespiratory capacity and actigraphy) and brain function [neuropsychological performance testing and neuroimaging (**cerebral blood flow (CBF)** and **brain volume**)] in older physically inactive PLWH at baseline and 26 weeks after randomization to either an EXS or a **social-interaction stretching (SIS)** program. In addition, we will obtain serum markers of neurogenesis, glucose regulation, and systemic inflammation.

D2 Subject Selection and Withdrawal

2.a Inclusion Criteria

1. age > or = 40 years old
2. documented history of HIV infection
3. on stable combination antiretroviral therapy (cART) for approximately 3 months with undetectable plasma HIV RNA
4. physically inactive-sedentary lifestyle (approximately <2 hours of exercise/week) and not engaged in regularly exercise for approximately 3 months prior to enrollment
5. approximately 9 years of education
6. able to have an MRI
7. able to provide written informed consent
8. all inclusion criteria at PI discretion

Exclusion Criteria

1. approximately >2x/week of moderate (or greater) exercise
2. cardiovascular/cerebrovascular disease or pulmonary disease that precludes ability to safely exercise
3. significant neurological disorders (e.g. stroke, head injury with loss of consciousness for >30 minutes, developmental learning disability
4. presence of dementia or behavioral disorders that would prevent ability to follow the protocol
5. alcohol or substance abuse/ dependence within the last 6 months (DSM-4 TR)
6. contraindications to MRI scanning (e.g. claustrophobia, pacemaker)
7. pregnant or breast-feeding
8. unable to provide written informed consent
9. currently taking anticoagulants or glucocorticoids
10. all exclusion criteria at PI discretion

2.b Ethical Considerations

All participants will receive an intervention, so no one will be receiving less care than another. Additionally, all participants will receive a free 6-month gym membership if they complete the study.

2.c Subject Recruitment Plans and Consent Process

Drawing on previous experience recruiting and maintaining a large cohort of PLWH at the WUSTL ACTG and ID Clinic, we understand the importance of fostering and maintaining an atmosphere of trust and cooperation among community leaders and agencies serving this group. Accordingly, the WUSTL ACTU and ID Clinic have established and maintained close alliances with HIV healthcare and community organizations. We will continue to draw upon these strong relationships in our recruitment efforts of the 58.3% of all PLWH in the St. Louis area who are ≥ 40 years of age. Targeted educational and recruitment in-services will be conducted with both WUSTL and outside community providers to ensure awareness of this project and to assist in identifying eligible participants.

The majority of HIV+ patients will come from referrals from community physicians and/or screening and evaluation procedures conducted at the WUSM AIDS Clinical Trial Unit and ID clinic, as well as from the Volunteers for Health Research Participant Registry. The records of the referred or other potential participants will be reviewed, either by paper copy or electronic method, (e.g., ClinDesk, Allscripts, etc.) for clinical information relevant to inclusion/exclusion criteria, including but not limited to age, HIV status, concomitant medical history, and current/past medications. If a patient appears to meet criteria, their name will be placed on a password- protected document/list/email and the treating clinician or case manager will be notified and asked to make first contact/obtain permission from the patient for us to contact them with information about the research project. If the treating clinician has recently seen the

patient or if the patient will not return for some time, study staff could contact the patient directly if his/her treating clinician agrees, in which case the patients will be told that their physician/resident/PA/APN, etc. has given permission for the research team to contact them. If the treating clinician indicates that this would not be an appropriate study subject, or if it becomes clear that the potential subject does not meet inclusion/exclusion criteria, or if the patient tells either the treating clinician or research staff that he/she is not interested in hearing about the study then there will be no further contact and their name will be removed from the list. With the gracious cooperation of the ACTU and other treating clinicians, several of this PI's other studies have used this method of referral and recruitment with great success. ACTU staff currently listed as engaged in this protocol may also speak with potential participants during study visits and refer them to us in a similar manner.

Once an individual is deemed eligible by the checklist above, individuals will be given a more detailed description of the study including possible risks and benefits, either over the phone or in person. Their medical records will be reviewed to fill in and confirm documented HIV+ status, undetectable viral load (VL), combination antiretroviral therapy (cART) and other medication regimens, presence of active cardiovascular/cerebrovascular or pulmonary disease or any other medical, or substance abuse/ dependence, that would meet exclusion criteria or make it unsafe to participate in any part of the study.

A study coordinator will discuss the research with the participants over the phone or in person and conduct a pre-screening assessment. For all participants, general health information will be reviewed for any contraindications to PET, CT and MR imaging. The participant's electronic health record (EHR) may be accessed in order to review any contraindications to planned study procedures, including PET, CT and MR imaging to confirm pre-screen eligibility. Prescreen eligibility will be confirmed and a consent form will be provided to the participant for review. Participants must be willing and able to undergo all procedures. Upon arrival to the imaging center, participants will be given adequate time to ask questions to ensure that any concerns are addressed prior to the consent process and study enrollment.

Subjects will then be brought in for written informed consent, urine drug screen, HIV dementia screen (HDS), Center for Epidemiologic Studies-Depression Scale (CES-D), and magnetic resonance imaging (MRI) questionnaire. The urine sample will be tested using the Rapid Drug screen (RDS) for amphetamines, cocaine, opiates, barbiturates, methamphetamines, benzodiazepenes, and phencyclidine. If a positive drug screen is observed, the participant will be rescheduled and baseline tests performed only when the RDS is negative. If the participant does <u>not</u> have dementia (HDS< 12), is <u>not</u> depressed (CESD < 24), and has <u>no</u> MRI contraindications; then s/he will continue with the baseline visit including: neurological/medical exam, NP testing and questionnaires (e.g. sleep, mood, exercise habits), and cardiorespiratory capacity testing. If an older PLWH is diagnosed with HAD (less than 5% of study population) using NP testing then this participant will be excluded as it less likely that this individual will be able adhere to the interventions. At the end of this visit, the subject will have an accelerometer secured to their non-dominant hand. The subject will be instructed to continue habitual physical activities. Approximately 2 weeks later, the subject will return for fasting laboratory studies and MRI. At the end of the baseline visit (week 0) the actigraph will be removed. Subjects who successfully complete this visit will be randomized to either <u>aerobic/resistance exercise</u> (EXS) or a <u>social-interaction stretching</u> (SIS) program.

At the end of 26 weeks, subjects will undergo 2 follow up visits, separated by approximately 1-2 weeks. The first follow-up visit after the study intervention will include: urine sample, neurological/medical exam, neuropsychological performance (NP) testing and questionnaires, and cardiorespiratory capacity testing. At the end of this first follow up visit, an actigraph will be secured to the non-dominant hand for approximately 1-2 weeks for collection of physical activity data. Approximately 1-2 weeks later, the subject will return for fasting laboratory studies and MRI.

Additional questionnaires looking at the physical, psychological, social and financial effects related to COVID19 will also be administered to provide information as to which parts of the brain may be most affected through their experiences (for example, increase in activity in the amygdala, the portion of the brain associated with emotional responses) and how that correlates with previous imaging, cognitive measures, and overall brain integrity. The COVID questionnaires will be administered at repeated timepoints by phone or via REDCap, and a waiver of written consent will be used for these assessments only. Study procedures and risks of the COVID questionnaires will be reviewed, and participants will have time to have all questions answered before beginning the questionnaires. Questionnaires will be assessed approximately every 3 months for approximately 1-2 years.

2.d Randomization Method and Blinding

All participants will be randomized in a 2(EXS):1(SIS) ratio by a computer program provided by co-investigator Dr. Florin Vaida either on or before the day of their Baseline (week -1) visit.

Neither participants nor study staff performing the assessments and scanning will know subjects' randomization; only staff performing the intervention, coordinator assigning the conditions and the PI will be un-blinded. Once their participation in the study has completely ended subjects may be informed of their randomization if they request.

2.e Risks and Benefits

There are potential risks associated with some of the procedures in this study. However, the procedures have been planned by the investigators to minimize the danger of any major complication. As with any study that collects sensitive information, breach of confidentiality is a potential risk, however, all study personnel will undergo training specific to the use of human participants in research, will be HIPAA-trained, and will be approved by the Institutional Review Board (IRB) to be engaged in the study. Only participant identification numbers (instead of PHI) will be used and all data and will be maintained according to the WUSTL School of Medicine and Health Insurance Portability and Accountability Act (HIPAA) "two lock" policy (i.e., locked data cabinets found in locked offices, password protected documents on password protected computers located in locked offices, etc.) No one other than study personnel will have access to this data.

Risks associated with neuropsychological performance testing and questionnaires:

Likely: None

Less likely: Subjects may experience fatigue, mental and/or emotional distress as a result of the questions that are asked during this testing. If a particular question makes a subject feel uncomfortable, s/he may discuss its importance with the specially trained interviewer. S/he may also choose not to answer any question with which s/he still feels uncomfortable.

Rare: None

Risks associated with magnetic resonance imaging (MRI): Subjects will be asked to inform study staff if they have any of the following: heart rhythm disturbances, cardiac pacemaker, aneurysm clip(s), implanted insulin/drug pump, neurostimulator (TENS unit), biostimulator/bone growth stimulator, hearing aid/cochlear implant, Gianturco coil (embolus coil), vascular clip(s), surgical clip(s) or staple(s), heart valve prosthesis, Greenfield vena cava filter, middle ear implant, penile prosthesis, shrapnel or bullet, wire sutures, tattooed eyeliner, any type of dental item held in place by a magnet, any other implanted item not mentioned, diaphragm/intrauterine device (IUD), intraventricular shunt, wire mesh, artificial limb or joint, any orthopedic item (i.e., pins, rods, screws, nails, clips, plates, wire, etc.), dentures, dental braces or any other type of removable dental items, or pregnancy.

Participants will be screened by MRI certified staff, including evaluation of metallic or electronic objects in or on their person, medical implants, tattoos, etc. using screening forms and workflows to reduce the risks listed below. If the participant experiences any the symptoms listed below and does not wish to continue, the study will be stopped immediately.

- Serious risk of injury from metallic objects pulled by the force of the magnet - For this reason, all persons entering the MRI environment must undergo standardized screening procedures;
- Serious risk of damage to electronic devices - The MRI staff will assess whether the research protocols are compatible with the FDA labeling of devices;
- Serious risk of burns - To reduce this risk, participants with tattoos or non-removable body piercings will need to undergo additional screening. Also, to reduce the risk of burns, participants are asked to change into clothing provided by the imaging facility;
- Low risk of tissue heating, with a possible rise in core body temperature;
- Low risk of hearing damage due to the loud noise of the MRI - Ear protection is required during the MRI scan;
- A low risk that participants will experience claustrophobia, which may manifest as anxiety, dizziness, or lightheadedness;
- Low risk of temporary muscle stiffness associated with lying still, which may be worse in patients with pre-existing arthritis;
- Low risk of peripheral nerve stimulation, which commonly manifests as muscle spasms.
- Rare risk that participants may experience a sensation of flashing lights while in the scanner.

Likely: If a subject has metal implants in his/her body (such as a pacemaker, or metal pin, or

shavings, etc.) s/he may be at risk when close to the machine. Subjects may experience heating or movement of the device, device malfunction, or damage to the tissue surrounding the device. Subjects could also experience claustrophobia (anxiety or nervousness while inside small spaces) when in the scanner, as well as stiffness from lying still for an extended period of time.

Less likely: The scanner produces a loud repetitive knocking noise during the study that some people find bothersome. If participants have skin tattoos, including cosmetic tattoos (i.e. eye liner, lip liner, etc.), they may experience irritation, swelling, or heating of the tattooed area, as well as potentially serious primary or secondary burns

Rare: Occasionally, some people may experience a short period of dizziness or feel faint after being in the scanner. There is also a rare possibility that a serious abnormality of which the subject is unaware may be discovered during the scan.

RISKS ASSOCIATED WITH BLOOD DRAW, FINGER STICKS & INTRAVENOUS LINE

Likely: Pain, stinging, bruising and bleeding at the site of needle insertion.
Less Likely: None
Rare: Infection at the site or blood clot.

RISKS ASSOCIATED WITH DXA Likely Mild • This study will expose you to radiation from the DXA scan. The amount of radiation from this, when averaged over your entire body, is 1/300 of the amount of radiation exposure all people in St. Louis receive each year from naturally occurring radiation sources. An additional DXA scan will increase exposure to radiation; however, when averaged over the entire human body, this is equivalent to less than 1 mrem, which can be categorized as less than 3% of the amount of natural background radiation exposure all people in St. Louis receive each year. The risk from the radiation exposure in this study is too small to be measured. It is not a big risk when compared with other risks you take every day. If you want to know more about radiation exposure, please see the 'Radiation Fact sheet' on the Research Participant section of the Human Research Protection Office website at http://hrpo.wustl.edu or ask the study staff for a copy.

Less Likely: None Rare: None

Risks associated with Exercise Stress Test (stationary bicycle stress test) and Exercise Fitness Test: Stress echocardiographic studies will be performed in the Cardiovascular Imaging and Clinical Research Core Laboratory (CRU), which is fully equipped with monitoring (blood pressure, 12-lead electrocardiogram (ECG), pulse oximetry) and emergency equipment (crash cart, intubation, and defibrillation equipment). A physician is immediately available at all times.

Likely: Subjects may experience shortness of breath and fatigue, as well as potential soreness from or injury to tendons, ligaments, joints, and muscles.

Less Likely: Discomfort from pressure from the echo probe may occur, as may redness or skin irritation from the electrodes used for the ECG.

Rare: Subjects may experience an increase in blood pressure, decrease in blood pressure, increases in heart rate, development of irregular heart rhythms, or chest pain.

Very Rare: An abnormal heart rhythm could develop that would require treatment with an electrical shock and/or a heart attack may occur. Heart attack (estimate 9 per 10,000 tests or < 0.1%) or death (estimate 2 per 10,000 tests or <0.02%) could occur.

Risks associated with Range of Motion Testing, Exercise and Stretching Training (aerobic/resistance training and stretching): During the past 15 years, over 500 men and women, who were 40-95 years old, have participated in the exercise-training research protocols at WUSTL without developing any significant problems.

Likely: Subjects may experience soreness or injury to tendons, ligaments, joints, and/or muscles.

Less Likely: Subjects may fall off of or injure themselves using equipment and may experience a break or strain/sprain. Study staff will be in the room with participants to monitor the work outs, however, there is always the possibility of an unforeseen accident. Subjects may also experience some mild skin irritation

from wearing the heart rate and blood pressure monitors, however, they can be adjusted to reduce their discomfort.

Rare: Development of ventricular arrhythmia, myocardial infarction, cardiac arrest, and death may occur. Although possible, we consider these events extremely unlikely. Repeated exercise testing of even highrisk patients (with known heart disease or with chronic kidney problems requiring dialysis) has been performed regularly at the WUSTL Human Applied Physiology Laboratory for the past 27 years without any major complications. During the past 15 years, as part of our ongoing research, we have performed maximal exercise tests on over 1,100 people in the 65 to 96 year age range, and performed multiple maximal exercise tests on more than 800 enrolled in our research projects without significant problems. In a large study of over 13,000 patients undergoing cardiac rehabilitation, the average complication rate was one non-fatal event for every 34,673 patient hours exercising, and one fatal event every 116,402 hours of exercise. Repeated exercise testing, when properly monitored under supervision of an experienced physician, does not appreciably increase the risk to the patient.

Risks associated with Focus Groups: Likely: None.

Less Likely: Since the study enrolls only HIV+ individuals, other group members will know that their fellow attendees are also HIV+. Participants may disclose confidential topics shared in group with others outside of the group, despite signing an agreement not to do so.

Rare: Subjects may feel uncomfortable or experience emotional distress regarding topics of discussion, but this will be minimized by reminding participants that the do not have to answer any questions/provide any information on topics with which they are not comfortable and by having a specially trained researcher available to debrief participants after the group ends.

All data will be safeguarded in accordance with HIPAA and the principles and practices of strict confidentiality. Studies are done for research purposes only. The risks of breaching confidentiality will be rigorously limited by the use of locked and restricted access to data as well as numbers rather than names will be used in the database for this project. No identifiers will be included in any computer files or reports generated by this study. All key personnel involved in the design or conduct of research that involves contact with human subjects will receive the required education on the protection of human research subjects prior to funding of this project.

The risks to subjects from the neuroimaging, NP evaluations and medical interview are minimal. Occasionally, the neurological examination or neuropsychological performance tests may induce anxiety or concern. This is usually controllable with appropriate counseling and explanation and ultimately by reminding subjects that the study is completely voluntary and that they are under no obligation whatsoever to participate. The risks of magnetic resonance imaging, specifically the danger of scanning an individual with metal in/on their person, will be virtually eliminated by having all subjects complete a metal screening sheet prior to their scans and by review of medical records to search for any confounds. Occasionally individuals experience anxiety and claustrophobic feelings during the scan procedure. Appropriate explanation is usually sufficient to allay anxiety, but again, volunteers will be reminded that they are free to stop the study at any time. All subjects will complete an exercise stress test (on a stationary bicycle) with continuous ECG monitoring and post-exercise echocardiography at the baseline study intervention follow-up visits. Any subject with evidence of serious cardiac abnormalities that increase the risk of starting an exercise program will be excluded from the study. Exercise testing, itself, when properly monitored, does not appreciably increase the risk to the subject. We have considerable experience in conducting exercise testing in high risk patients (with ischemic heart disease or on chronic renal dialysis), have performed maximal exercise tests in more than 1100 people who were 65 to 96 years old, and performed multiple maximal exercise tests on more than 800 enrolled in our research projects without any significant problems.

Exercise training will be led by a certified fitness professional. All subjects will wear a heart rate monitor during exercise to monitor their exertion. Exercise will be individualized based on the results of a movement screening, to prevent musculoskeletal injury. In the unlikely case of a cardiac event, there is an emergency plan in place at the Exercise Training Facility; there is an AED located in the facility and medical staff is immediately available.

Only highly trained research staff, nurses, and physicians will be utilized to collect data. These individuals will be experts in confidential and professional interaction with study subjects. Subjects will be notified in the informed consent document that any serious suicidal or homicidal information obtained will be shared as necessary with appropriate authorities to protect the life of the subject. If a subject is found to be suicidal or homicidal during any evaluation, the individual performing the evaluation will take immediate

suicide and homicide precautions, contacting the PI, study physician, subject's primary physician and any authorities necessary to insure safety. If the subject is the sole adult household member and suicide/homicide is not deemed to be imminent, precautions and referrals, including emergency room contacts, will be provided. If any subject is deemed to be imminently suicidal and/or homicidal, 911 will be contacted as soon as possible. Subjects will also be told in the informed consent document that research staff will provide a request for a referral for professional care as necessary. To protect against any misuse of knowledge about study participation, the informed consent document will advise potential subjects that employers or insurers could act negatively if they learned of participation in this study. Subjects may choose not to disclose their participation to these entities.

All MRI scans are reviewed by a radiologist. If there is a clinically meaningful abnormality identified or other medical need for sharing of the standard clinical MRI portion of the exam, workflows have been established for sharing the images and reports. Any potentially clinically meaningful abnormal findings are communicated to the participant by the Principal Investigator or a designee and, if the participant permits, to their physician. If requested for clinical use, and following hospital HIPAA policies, a copy of the participant's MRI scan and report can be uploaded into the participant's electronic health record (EHR). Once the MRI is part of the EHR, then participants may request additional copies to be sent to additional physicians using a standard medical record request.

Research team members conducting the focus groups will be trained specifically for that purpose, with particular emphasis on managing confidentiality and privacy both amongst group members and in respect to storing the data. All notes taken and recordings made during the group will be kept according to strict WUSTL HIPAA standards under the "2- lock" rule. Participants will be reminded that only the researchers will have access to their data, but that they also have a responsibility of keeping information discussed within the group confidential and not to converse about it outside of the group so that all members may feel safe in their self-expression. As an added measure of protection, group members will be asked to provide written informed consent and sign a confidentiality agreement to this effect before engaging in any group discussions. Since this study includes only PLWH, group participants will be notified of this before they commit to attending the group so they understand that while the study staff will never release their status, others participating in the group will know their status and may disclose this information to people outside of the group even though asked not to do so. For this reason, the names of group attendees will only be known to research staff and not to others attending the group, however, attendees that already know each other prior to enrolling in the study may still be at risk for having their status revealed.

2.f Early Withdrawal of Subjects

Participants will be reminded that they can withdraw their consent and drop out of the study at any point without being subject to retribution or any effects on their medical care. If subject chooses to drop out early or is withdrawn from the study, they will be invited to complete the follow-up evaluations (neuropsychological testing and questionnaires, MRI, cardiorespiratory capacity testing, fasting labs,neuromedial exam, actigraph measurement and stool sample) at that time. Should anyone's participation pose a risk after they have already begun the intervention, subjects will be evaluated on a case-by-case basis by the study team to determine if it is safe for them to continue in the study or should be withdrawn for their safety.

2.g Data Collection and Follow-up for Withdrawn Subjects

Once a participant has been withdrawn from the study, either voluntarily or by study staff, no more data will be collected and follow-up will be provided as needed on a case-by-case basis. If a participant is withdrawn and then wants to get back in the study, s/he must be re-consented before any further study procedures are conducted.

D3 Study Intervention

3.a Description

After completing all screening assessments, subjects will be randomized in a 2:1 ratio (EXS:SIS) into one of the following 2 conditions:

EXS: All EXS sessions will be conducted at an indoor exercise facility at the WUSTL medical campus. Two sessions will be offered per weekday and will contain 10-12 participants. Each session will start with 5-10 min range of motion exercises. Participants will then follow his/her

individualized exercise training prescription based on baseline cardiovascular testing. Individual aerobic exercise intensity will be based on a percent of maximum heart rate (HRmax) achieved during the baseline cardiorespiratory fitness test (week -1). The target exercise HR will start at 50% and progress to 85% HR reserve (i.e., moderate to high intensity). During aerobic exercise, HR will be monitored by a battery-operated HR monitor (Polar, Lake Success, NY). HR and time spent exercising at target HR will be stored and documented daily to verify adherence and to calculate aerobic exercise energy expenditure. Exercise intensity (target HR) and duration (from 10 min up to 40 min) will be progressively increased as the participant acclimates to the exercise prescription. Adaptation will be determined when a given exercise intensity yields a lower HR than prior exercise sessions conducted at the same exercise intensity or the participant has a lower perceived exertion. The trainer will interact with each participant during their individualized exercise training and will provide feedback to ensure an appropriate rate of progression.

The resistance exercise training component will follow aerobic exercise and will consist of four upper and three lower body routines (chest press, elbow flexion, latissimus dorsi pull down, triceps press, knee extension, knee flexion, and leg press). A combination of guided-motion machines and free weights will be used. Baseline voluntary maximum strength (1 repetition maximum) will be measured during the first 4 exercise sessions on each exercise station. Resistance training program will initially consist of 1-2 sets of each exercise while lifting a weight that causes muscle fatigue after 8-10 repetitions. A rest period of 2 seconds will be given between repetitions, 1–2 minutes between sets, and 2–4 minutes between each exercise. The trainer will monitor each participant's exercise response, and when the participant can comfortably lift the weight for 12 repetitions on any exercise, the weight (intensity) will be increased (~10%) to cause the muscle group to fatigue after 8 repetitions. This progressive 8-12 repetition cycle is repeated for each exercise over the 26 weeks. Energy expended during resistance exercise will be calculated as weight lifted x number of repetitions completed x distance the weight lifted. Total energy expended over the 26 weeks for the EXS program will be calculated.

SIS: This group will serve as a control group against which to gauge the effects of aerobic and resistance training on cognitive function. Participants in this group will follow the same schedule and format as the EXS group. These participants will also be supervised by the trainer and will receive similar amounts of attention and class interaction as participants in the EXS program. These SIS participants will receive evaluation/instructions on stretching, range of motion, limbering, and toning; but the intensity will be far less than that achieved in the EXS classes. Activities will focus on socialization and flexibility enhancement. As the participant's level of flexibility increases, stretches with increasing levels of difficulty will be incorporated into the program.

At any time, participants may be asked to wear heart rate and blood pressure monitors while in the gym, whether for the SIS or EXS condition. Participants with a history of diabetes may also be asked to do one of more finger sticks at each session to monitor blood sugar levels.

At least once per month but possibly more frequently, the SIS group will have their range of motion measured, and the EXS group will have their one-rep max weight measured to gauge progress throughout the intervention.

3.b Treatment Regimen

Subjects will be asked to come in approximately 3x per week for 26 weeks to perform the exercise regimen associated with the group to which they have been randomized. Transportation via taxi or provision of Metro tickets will be provided as necessary. Participants may choose to be paid weekly ($15/week) during the intervention or have paid at the end in one lump sum ($ 390).

While there will likely be more than one participant at the exercise facility at a time, the trainer will be walking around, surveying each participants' effort and ability, adjusting the settings on the machines/amount of weight to be lifted/exercises to be done on a case-by-case basis in real time. The trainer will also monitor the vital signs of all participants as they exercise to insure subject safety and will end a session and call one of the study physicians for an evaluation should there be a concern.

Subject Compliance Monitoring

The trainer(s) will keep track of all participants' attendance and provide it to the coordinator for feedback and to follow up with subjects that have not been compliant with their study visits.

3.c Blinding of Treatment Condition

Only the PI, study coordinator and exercise trainers will know to which group participants have been randomized. Subjects will be informed of their treatment condition only after they complete their participation, and all staff involved in collecting and processing data and/or performing statistical analyses will be blinded. Should an emergency medical or safety concern arise, however, randomization schemes will be readily accessible to any study staff necessary to insure and prioritize patient well-being.

E Study Procedures

E1 Screening for Eligibility

Pre-consent screening (done through review of medical records and/or discussion with subject) to insure subject DOES meet the following criteria:

1. age ≥ 40 years old
2. documented history of HIV infection
3. on stable combination antiretroviral therapy (cART) for approximately 3 months with undetectable plasma HIV RNA
4. physically inactive-sedentary lifestyle (approximately <2 hours of exercise/week) and not engaged in regularly exercise for approximately 3 months prior to enrollment
5. approximately 9 years of education
6. able to have an MRI
7. able to provide written informed consent (does not have LAR, POA, etc.)

and DOES NOT meet the following criteria:

1. approximately >2x/week of moderate (or greater) exercise
2. cardiovascular/cerebrovascular disease or pulmonary disease that precludes ability to safely exercise
3. significant neurological disorders (e.g. stroke, head injury with loss of consciousness for >30 minutes, developmental learning disability
4. presence of dementia or behavioral disorders that would prevent ability to follow the protocol
5. alcohol or substance abuse/ dependence within the last 6 months (DSM-4 TR)
6. contraindications to MRI scanning (e.g. claustrophobia, pacemaker)
7. pregnant or breast-feeding
8. currently taking anticoagulants or glucocorticoidsd
9. unable to provide written informed consent

E2 Schedule of Measurements

E3 Pre-Consent Screening

1. DOB/age (must be 40 years of age or older to qualify)
2. Length of time on cART (must be approximately > or = to 3 months to qualify)
3. Number of hours of exercise per week (must be approximately <2 hours/week to qualify)
4. Number of months engaged in regular exercise (must be < than approximately 3 months prior to enrollment)
5. Number of years of education (must be > or = 9 years to qualify)
6. History of claustrophobia, serious head injuries, seizures, developmental delays, pregnancy, pacemaker, metal implants, permanent metal piercings, or any other condition that could make MR imaging unsafe.

. **B) Review of Medical Records** (to verify subjects' responses to pre-screening questions and make sure meet inclusion/exclusion criteria). Medical records, including but not limited to HIV/AIDS-related outpatient visits, inpatient hospitalizations, blood/diagnostic/laboratory/imaging tests, substance use/abuse/dependence, mental health treatment, and cardiovascular history/events/surgeries will be obtained from participants' health care providers. Additional information may also be obtained from clinical interviews or questionnaires found in participants' records related to their medical care. The names/contact information/DOB of these individuals will also be collected. The

research team may also review the subject's research records from other WUSM studies. This will allow the research team to determine/clarify eligibility. Also, additional labs necessary for the VACS Index (CD4, VL, HCV, AST, ALT, hemoglobin, platelets, fibrinogin-4, creatinine and GFR) drawn within approximately the past 12 months will be reviewed.

E4 Screening Visit

1.Review of medical records (if not done previously)
2. Provision and documentation of written informed consent
3. UDS
4. Pregnancy test (1 or 2, depending on appointment schedules)
5. HIV Dementia Scale (HDS)
6. CES-D depression scale
7. MRI questionnaire

E5 Baseline Visit(s) (can be performed same day as screening visit)

1. Neuromedical exam
2. History & physical
3. Vital signs (BP, HR, height, weight, waist circumference)
4. Assessments, questionnaires, & other evaluations:
   NEUROPSYCHOLOGICAL ASSESSMENTS: 1. BVMTR (Bender Visual Motor Gestalt Test -- evaluates visual-perceptual and visual-motor functioning, yielding possible signs of brain dysfunction, emotional problems, and developmental maturity) 2. Hopkins Verbal Learning Test (HVLT -- measure of verbal episodic memory) 3. Trailmaking Parts A and B (measure attention, visual searching, mental processing speed, and the ability to mentally control simultaneous stimulus patterns) 4. Digit-Symbol Substitution Task (measures brain damage, dementia, age and depression) 5. Grooved Pegboard dominant and non-dominant hand (Measures performance speed in a fine motor task. By examining both sides of the body, inferences may be drawn regarding possible lateral brain damage.) 6. Letter-Number Sequencing (tests working memory and attention) 7. Wide Range Achievement Test (3 or 4) (Provides level of performance in reading, spelling, and written arithmetic. The reading and spelling tests are often used in estimating premorbid intellectual functioning.) 8. Timed Gait (standardized procedure assessing motor dysfunction of lower extremities and gait abnormalities associated with AIDS dementia complex) 9. Finger Tapping (measures motor speed) 10. FAS (measures executive cognitive dysfunction) 11. Category Fluency (animals) (tests executive functions and language, as well as semantic memory) 12. Action Fluency (examines verbally mediated executive functions, especially frontal system damage) 13. Stroop Interference Test (tests switching, cognitive flexibility and inhibition) 14. WAIS-III Symbol Search (tests perceptual organization and processing speed) 15. Iowa Gambling Task (computer exercise) (assessment of risk-taking) 16. Medication Management Task (listed as perf meas 1-5 on attachments) 17. Boston Naming Test (measures ability to retrieve words/language disturbance) 18. Digit Span (tests visuospacial and attention domains) 19. Line Orientation (tests visuospacial and attention domains) 20. Rey-Osterrieth Complex Figure Test [Rey-O] (assesses visuospatial abilities, memory, attention, planning, and working memory) 21. Wisconsin Cart Sorting Task [WCST -- computerized] (assesses executive functioning planning use of feedback and shifting) 22. Paced Auditory Serial Addition Task [PASAT] (assessment of speed of information processing) 23. Montreal Cognitive Assessment [MOCA] (screening assessment for mild cognitive impairment) 24. Virtual Week (computerized prospective and retrospective memory assessment)

   QUESTIONNAIRES: 25. Lawton & Brody ADL scale (assessment of ability to independently perform activities of daily living) 26. SES questions (looks at subjects' socioeconomic status, as well as previous early life trauma they may have experienced) 27. Risk Assessment Battery (assessment of risk-taking) 28. Beck Depression Inventory (records symptoms of depression subjects have had in the past 2 weeks) 29. KMSK (Kreek-McHugh-Schluger-Kellogg scale -- designed to quantify self-exposure to opiates, cocaine, alcohol,tobacco and/or marijuana) 30. Fagerstrom smoking questions (corrected version) (scale of nicotine dependence) 31. Locator Form (basic contact information, physicians' names, etc.; zip code will be used not only to contact participants, but also to determine median

income for the area in which they live for data analyses) 32. Pittsburgh Sleep Quality Index (assesses sleep quality and disturbances over a 1-month interval) 33. ADL questionnaire (questionnaire of ability to perform activities of daily living) 34. Prospective and Retrospective Memory Questionnaire (PRMQ). 35. International Physical Activity Questionnaire (IPAQ) 36. Substance Use Social Disruption Questions (assessing social disruption from drugs and/or alcohol)

ADDITIONAL ASSESSMENTS: 1. Fried Frailty Assessment 2. Calculation of the VACS index (captures both HIV and aging hallmarks to predict comorbidity and mortality) 3. Patient Centered Assessment and Counseling for Exercise (PACE) (assesses attitudes about exercise, barriers/facilitators to adherence to EXS, exercise enjoyment, self-efficacy and social support); 4. Charlson Comorbidity Index

5. Cardiorespiratory capacity testing (including stationary bicycle workout (VO2 test), DXA & 6 minute walk test). An intravenous line may be placed in the participant's arm. This line may be kept in place for several hours during the cardiovascular evaluation for safety monitoring.
6. Attachment of actrigraph at end of visit. Participants will wear the actigraph for approximately 1-2 weeks before and 1-2 weeks after the intervention. They may also be asked to wear it for some duration during the intervention, anywhere from approximately 1 week to the entire intervention.
7. Randomization in a 2:1 ratio to either the Exercise intervention (N=100) or the Social Interaction/Stretching intervention (N=50)
8. Collection of fasting labs (such as but not limited to CMP, sCRP, CBC w/diff, HbA1C, leptin, D-Dimer, YSI, Insulin/IFG-1/C-peptide/Glucagon, plasma BDNF, plasma VEGF, Adiponectin, IL-6, HOMA-IR/fasting glucose & insulin, glycosylated hemoglobin, plasma IGF-1, soluble CD163, plasma neopterin, galectin 9, etc.) and APOE test (APOE will only be done at baseline, not at follow up). CD4 and VL may also be collected if not available through medical records, and approximately 32 6of blood will also be taken and banked for future use as documented in the Informed Consent.
9. 3T MRI lasting approximately 1 hour
10. Stool sample and dietary survey.
11. Scheduling of dates/times to attend intervention**.**

E6 Intervention approximately 3x per week for 26 weeks

1. **Subject will be able to make up visits, if missed (i.e. If subject comes in 2x during 1 week, they can come 4x the next week for an average of 3x per week).**

E7 1 month stool sample and dietary survey

1. Participants will also be given a stool collection kit and asked to bring samples in at baseline, 1 month, mid-point (approx. 3 months), and final follow-up (approx. 6 months). They will also be asked to complete a dietary survey such as the ASA24 or 24 hour food log each time a stool sample is provided.

E8 Midpoint Assessment

1. Assessments, questionnaires, & other evaluations:
NEUROPSYCHOLOGICAL ASSESSMENTS: 1. BVMTR (Bender Visual Motor Gestalt Test -- evaluates visual-perceptual and visual-motor functioning, yielding possible signs of brain dysfunction, emotional problems, and developmental maturity) 2. Hopkins Verbal Learning Test (HVLT -- measure of verbal episodic memory) 3. Trailmaking Parts A and B (measure attention, visual searching, mental processing speed, and the ability to mentally control simultaneous stimulus patterns) 4. Digit-Symbol Substitution Task (measures brain damage, dementia, age and depression) 5. Grooved Pegboard dominant and non-dominant hand (Measures performance speed in a fine motor task. By examining both sides of the body, inferences may be drawn regarding possible lateral brain damage.) 6. Letter-Number Sequencing (tests working memory and attention) 7. Finger Tapping (measures motor speed) 8. FAS (measures executive cognitive dysfunction) 9. Action Fluency (examines verbally mediated executive functions, especially frontal system damage) 10. Stroop Interference Test (tests switching, cognitive flexibility and inhibition) 11. Digit Span (tests visuospacial and attention domains) 12. Rey-Osterrieth Complex Figure Test [Rey-O] (assesses visuospatial

abilities, memory, attention, planning, and working memory) 13. Wisconsin Cart Sorting Task [WCST -- computerized] (assesses executive functioning planning use of feedback and shifting) 14. Paced Auditory Serial Addition Task [PASAT] (assessment of speed of information processing) 15. Montreal Cognitive Assessment [MOCA] (screening assessment for mild cognitive impairment)

QUESTIONNAIRES: 16. Beck Depression Inventory (records symptoms of depression subjects have had in the past 2 weeks) 17. KMSK (Kreek-McHugh-Schluger-Kellogg scale -- designed to quantify self-exposure to opiates, cocaine, alcohol,tobacco and/or marijuana) 18. ADL questionnaire (questionnaire of ability to perform activities of daily living) 19. Substance Use Social Disruption Questionnaire (assessing social disruption from drugs and/or alcohol)

ACTIGRAPHY: Actigraph may be re-attached for approximately 1-2 weeks around the time of the midpoint assessment.

Stool sample and dietary survey.

E9 **Re-screening Visit**

1.Review of medical records (if not done previously)
2. Provision and documentation of written informed consent
3. UDS
4. Pregnancy test
5. HIV Dementia Scale (HDS)
6. CES-D depression scale
7. MRI questionnaire

E10 **Follow-Up Visit(s)** (can be performed same day as re-screening visit)

1. Neuromedical exam
2. History & physical
3. Vital signs (BP, HR, height, weight, waist circumference)
4. Assessments, questionnaires, & other evaluations:
   NEUROPSYCHOLOGICAL ASSESSMENTS: 1. BVMTR (Bender Visual Motor Gestalt Test -- evaluates visual-perceptual and visual-motor functioning, yielding possible signs of brain dysfunction, emotional problems, and developmental maturity) 2. Hopkins Verbal Learning Test (HVLT -- measure of verbal episodic memory) 3. Trailmaking Parts A and B (measure attention, visual searching, mental processing speed, and the ability to mentally control simultaneous stimulus patterns) 4. Digit-Symbol Substitution Task (measures brain damage, dementia, age and depression) 5. Grooved Pegboard dominant and non-dominant hand (Measures performance speed in a fine motor task. By examining both sides of the body, inferences may be drawn regarding possible lateral brain damage.) 6. Letter-Number Sequencing (tests working memory and attention) 7. Wide Range Achievement Test (3 or 4) (Provides level of performance in reading, spelling, and written arithmetic. The reading and spelling tests are often used in estimating premorbid intellectual functioning.) 8. Timed Gait (standardized procedure assessing motor dysfunction of lower extremities and gait abnormalities associated with AIDS dementia complex) 9. Finger Tapping (measures motor speed) 10. FAS (measures executive cognitive dysfunction) 11. Category Fluency (animals) (tests executive functions and language, as well as semantic memory) 12. Action Fluency (examines verbally mediated executive functions, especially frontal system damage) 13. Stroop Interference Test (tests switching, cognitive flexibility and inhibition) 14. WAIS-III Symbol Search (tests perceptual organization and processing speed) 15. Iowa Gambling Task (computer exercise) (assessment of risk-taking) 16. Medication Management Task (listed as perf meas 1-5 on attachments) 17. Boston Naming Test (measures ability to retrieve words/language disturbance) 18. Digit Span (tests visuospacial and attention domains) 19. Line Orientation (tests visuospacial and attention domains) 20. Rey-Osterrieth Complex Figure Test [Rey-O] (assesses visuospatial abilities, memory, attention, planning, and working memory) 21. Wisconsin Cart Sorting Task [WCST -- computerized] (assesses executive functioning planning use of feedback and shifting) 22. Paced

Auditory Serial Addition Task [PASAT] (assessment of speed of information processing) 23. Montreal Cognitive Assessment [MOCA] (screening assessment for mild cognitive impairment) 24. Virtual Week (computerized prospective and retrospective memory assessment)

QUESTIONNAIRES: 25. Lawton & Brody ADL scale (assessment of ability to independently perform activities of daily living) 26. SES questions (looks at subjects' socioeconomic status, as well as previous early life trauma they may have experienced) 27. Risk Assessment Battery (assessment of risk-taking) 28. Beck Depression Inventory (records symptoms of depression subjects have had in the past 2 weeks) 29. KMSK (Kreek-McHugh-Schluger-Kellogg scale -- designed to quantify self-exposure to opiates, cocaine, alcohol,tobacco and/or marijuana) 30. Fagerstrom smoking questions (corrected version) (scale of nicotine dependence) 31. Locator Form (basic contact information, physicians' names, etc.; zip code will be used not only to contact participants, but also to determine median income for the area in which they live for data analyses) 32. Pittsburgh Sleep Quality Index (assesses sleep quality and disturbances over a 1-month interval) 33. ADL questionnaire (questionnaire of ability to perform activities of daily living) 34. Prospective and Retrospective Memory Questionnaire (PRMQ). 35. International Physical Activity Questionnaire (IPAQ) 36. Substance Use Social Disruption Questionniare (assessing social disruption from drugs and/or alcohol)

ADDITIONAL ASSESSMENTS: 1. Fried Frailty Assessment 2. Calculation of the VACS index (captures both HIV and aging hallmarks to predict comorbidity and mortality) 3. Patient Centered Assessment and Counseling for Exercise (PACE) (assesses attitudes about exercise, barriers/facilitators to adherence to EXS, exercise enjoyment, self-efficacy and social support)

5. Cardiorespiratory capacity testing (including stationary bicycle (VO2 test), DXA and 6 minute walk test)
6. Attachment of actrigraph at end of visit (if subject hasn't been wearing it throughout the intervention).
7. Removal of actigraph at last follow up appointment
8. Fasting labs (such as but not limited to CMP, sCRP, CBC w/diff, HbA1C, leptin, D-Dimer, YSI, Insulin/IFG-1/C-peptide/Glucagon, plasma BDNF, plasma VEGF, Adiponectin, IL-6, HOMA-IR/fasting glucose & insulin, glycosylated hemoglobin, plasma IGF-1, soluble CD163, plasma neopterin, galectin 9, etc.) and APOE test (APOE will only be done at baseline, not at follow up). CD4 and VL may also be collected if not available through medical records.
9. 3T MRI lasting approximately 1 hour
10. Stool sample and dietary survey.
11. Distribution of gym membership

If any of the testing procedures listed above have been completed recently (as determined by PI discretion) as part of another research study in which the subject has participated, data from those studies may be used as data for this study so as to not have the subject unnecessarily repeat procedures/create additional participant burden.

E11 Remote Visit:

Previously consented and enrolled participants will be contacted by phone to complete additional questionnaires regarding their experiences during the COVID-19 pandemic. Participants will have the option to complete the questions online through a RedCap generated survey or over the phone. The time to complete will vary, with an approximate duration of 1.5 hours. Questionnaires will be assessed approximately every 3 months for approximately 1-2 years.

Questionnaires:

- Florida COVID-19 Experiences
- Florida COVID-19 Stress
- HCP Symptoms and Medical Care Survey
- Florida COVID-19 Behaviors
- NIH Toolbox Emotion NIH TB Self-Efficacy CAT Age 18+

- Rotter's Locus of Control Scale
- International Physical Activity Questionnaire
- NIH Toolbox Emotion NIH TB Instrumental Support SF Age 18+
- Beck Depression Inventory
- Hospital Anxiety and Depression Scale (HADS
- UCLA Loneliness Scale
- KMSK
- KMSK Social Disruption Scale
- Pittsburgh Sleep Quality Index
- NIH TB Perceived Stress CAT Age 18+
- HCP Financial Impact

E12 Safety and Adverse Events

All safety monitoring and reporting will be conducted in accordance with WU HRPO policies.

Data and Safety Monitoring Board

This protocol will include adverse event and other reporting by the PI and study coordinator to the Data and Safety Monitoring Board (DSMB). The conduct of this study will be reviewed annually by the DSMB. The DSMB will consist of: 1) Dr. Serena Spudich (Yale)- expert in neuroAIDS and HAND clinical trials; 2) Dr. Richard Buxton (UCSD)- expert in exercise physiology/neuroimaging; 3) Dr. Kenneth Schechtman (WUSTL)- statistician with expertise in exercise clinical; 4) Dr. John Morris (WUSTL)- an expert in aging and Alzheimer's disease clinical trials; and 5) program officer from NIH funding institute.

Serious adverse events will be reported to the IRB. The stopping criteria and guidelines to be used for this protocol will include the following: 1) The study will be stopped if there is clear evidence of harm or harmful side effects of the procedures used in this protocol; 2) In the event that a serious adverse event (SAE) occurs that increases the risks to participants, the study will be stopped and an investigation will be conducted and a findings report generated the PI and DSMB; 3) Should there be SAE or adverse event (AE) that occur at a frequency greater than 5%, it will be added to the consent document, if not already addressed and enrollment will be halted while a determination is made regarding the potential risks to participants. The risks of the intervention in this study population are low, however, the DSMB will review safety material.

Definitions and Reporting Guidelines and Timelines of Adverse Events

Same as defined by HRPO.

F Statistical Plan

Statistical Plan

Aim 1: Hypothesis 1a. Primary Analysis of the Study: We will assess if an EXS program in older sedentary PLWH enhances core NP domains (executive function, attention, and memory) compared to a SIS program. The change from baseline to 26 weeks after study intervention for each core domain Z- score and global Z-scores (comprised of the three core cognitive domain Z scores) will be compared between the EXS and SIS groups using t-tests. A 0.5 SD change in global Z-score is considered a clinically meaningful improvement and is currently being used for a pharmacotherapy (maraviroc) trial for HAND 149. In the present trial we anticipate that an EXS program will lead to >0.5 SD change in global Z-scores but we recognize that the precise threshold for individual perception of improvement is variable. For this analysis will use all random-ized subjects, under the intent-to-teat (ITT) paradigm. For participants missing a 26 week endpoint, a value will be imputed based on the lower (worse) half of the distribution from their arm (conservative approach).

Secondary analyses: Mean change in supplementary domain Z-scores at 26 weeks will be compared between the EXS and SIS groups for all randomized participants using the Z-test, under the following scenarios: (a) As treated (AT), with all subjects for whom the endpoint is available included in their allocated group; and (b) Per-protocol (PP), including only adherent participants (≥80% of study visits) for whom the 26 week endpoint is available. Additional multivariable secondary analyses will adjust for demographic and other rele-vant predictors, including plasma viral load and nadir CD4, gender,

depression, and other potential predictors that are significantly associated with the outcome at the 0.15 level using a backward model selection. In partic- ular, the inclusion of gender and depression will allow for identification of differential changes in NP for men and women, and indirect effects of exercise mediated by depression 150-152. Since this is a medium-size ran-domized study we expect the unadjusted analysis to yield an unbiased estimate of the treatment effect. The outcomes will be collected only at baseline and follow-up, so a longitudinal analysis using generalized estimat-ing equations or mixed effects models is not necessary as it would yield essentially identical results.

Principal Stratification (PS) Analysis: An additional exploratory secondary analysis will be done using a Principal Stratification framework 153. This analysis compares the treatment arms separately for four subsets determined by whether participants would adhere to the study on any of the two study arms or not. According-ly, the four sets are: adherers on both EXS, SIS; non-adherers on both EXS, SIS; adherers on EXS but not on SIS; adherers on SIS but not on EXS. In practice these data are available for only one of the two statuses that the subject is randomized to, but the second status is effectively imputed statistically. This innovative analysis will allow for separate evaluation of effects of EXS intervention for those who can and those who cannot adhere to the exercise plan, and will give insights into the differential effectiveness of the EXS program.

Hypothesis 1b: We will assess if greater improvements in physical function due to an EXS program are associ-ated with better cognitive performance. We will test the mediating effect of improvements in physical function on cognitive performance in two ways: (i) between randomized groups, and (ii) within the EXS group. Linear models will be used to determine the mediating effect of the physical function markers (high/low physical ac-tivity and peak VO2) on the change from baseline in core domain specific Z-scores and the global Z-score, by including these markers, together with group assignment, as predictors in the model. Within the EXS group similar linear models will be fit (without the group variable). Similar analyses for supplemental Z-score do- mains will be explored in secondary analyses.

Exploratory analyses: A similar analysis will be conducted, (i) including both groups, and (ii) within the EXS group, evaluating the mediating effects of changes in glucose regulation (fasting glucose and HOMA-IR) and chronic inflammation (hsCRP, D-dimer, IL-6) on cognitive endpoints. Other variables to be assessed include neurogenesis factors (BDNF, IGF-1, and VEGF). Additional analyses will control for relevant predictors, using a backward model selection strategy as described above.

Aim 2. Hypothesis 2a. Primary Analysis of the Study: We will assess if an EXS program improves brain struc-ture and function more than a SIS program in older sedentary PLWH. Changes in brain volumetrics (hippo-campus, caudate, and anterior cingulate) and regional CBF (hippocampus, caudate, and anterior cingulate) at baseline and 26 weeks will be compared between EXS and SIS groups using a similar design as for Aim 1, in-cluding ITT, AT, and PS analyses. The brain imaging outcomes will be adjusted for the relevant markers of brain size. A Holm-Bonferroni correction will be used when evaluating the brain volumetrics across the differ-ent regions 154.

Secondary analyses: Similar analyses will also be performed for brain volumetrics and regional CBF in the amygdala, thalamus, and putamen. Additional analyses will control for relevant predictors, using a backward model selection strategy, as mentioned above.

Hypothesis 2b: We will assess if greater improvements in physical function due to EXS are associated with larger brain volumetrics and increases in regional CBF. We will test the mediating effect of improvement of physical function on neuroimaging measures in two ways: (i) between randomized groups, and (ii) within the EXS group. Linear models will be used to determine the mediating effect of the physical function markers (high/low physical activity and peak VO2) on the change from baseline in structural and functional neuroimag-ing measures, by including these markers, together with group assignment, as predictors in the model. Within the EXS group similar linear models will be fit (without the group variable).

Hypothesis 2c. We will assess if greater improvements in cognition are associated with improved brain struc-ture and function changes. Linear models will examine the relationship between neurocognitive performance (outcome) and brain structural and functional changes (predictors), using only the 100 participants random-ized to the EXS group. These models will adjust for potential confounders, (e.g. plasma viral load and nadir CD4) that are significantly associated with the outcome at the 0.15 level using backward model selection.

Exploratory analyses: A similar analysis will be conducted, (i) including both groups, and (ii) within the EXS group, evaluating the mediating effects of changes in glucose regulation (fasting glucose and HOMA-IR) and chronic inflammation (hsCRP, D-dimer, IL-6) on neuroimaging endpoints. Other variables that will also be as-sessed include neurogenesis factors (BDNF, IGF-1, and VEGF). Additional analyses will control

for relevant predictors, using a backward model selection strategy, as mentioned above.

Secondary endpoints: Scores from questionnaires that assess stage of behavior change, social support, self-efficacy, and exercise enjoyment will be incorporated with other quantitative outcome data. Logistic re-gression analyses will be conducted with response variables including: 1) successful complete (Y/N) 2) posi-tive changes in cognitive function (Y/N); 3) positive change in brain structure and function (Y/N). The pre-dictors will be the psychosocial or implementation factor scores. Odds ratios will be computed adjusting for demographic and other characteristics using backward model selection, as discussed before.

Additional Analyses: Baseline characteristics: Baseline demographic, medical, implementation factors, and lab characteristics of participants will be summarized by intervention arm (EXS or SIS) using N (%) for categorical variables, and mean, standard deviation, and range for numeric variables. Between-arms comparisons will use Fisher's exact test (FET) and Wilcoxon rank-sum test (WRST) for categorical and numeric variables, respectively. Neuroim-aging comparisons will be adjusted via an analysis of covariance for measures of intra-cranial volume.

Study enrollment and drop-out: The number (%) of participants randomized, N (%) of participants com-pleting 26 weeks, and N (%) of patients lost to follow-up will be summarized overall and by treatment arm, and compared between treatment arms using FET. For participants lost to follow-up we will record dates and rea-sons (if known) for loss to follow-up. Baseline demographic and medical characteristics will be compared be-tween dropouts and completers using FET and WRST for categorical and numeric variables, respectively.

Adherence and discontinuation: Adherence to either program will be calculated as the percentage of ses-sions attended out of a possible of 78 sessions. A participant in either arm will be considered adherent if s/he attends 80% or more (or 63) of the total scheduled visits. The number (%) of adherent participants will be summarized overall and by treatment arm, and will be compared using FET.

Lab abnormalities: Participants with lab abnormalities will be tabulated and summarized by treatment arm. The number of participants with serious abnormalities will be compared between arms using FET. Adverse events: N (%) participants with adverse events will be tabulated and summarized overall and by treatment arm, with grade of the event included. The study week and reasons for adverse events will be includ-ed. The number of participants with grade ≥3 adverse events will be compared between arms using FET.

Power Analysis for Specific Aim 1: With 150 randomized subjects we have 80% power to detect an effect size (Cohen's d) = 0.49 in the primary ITT analysis. Anticipating a 20% drop-out rate at 26 weeks (80 EXS + 40 SIS) we will have 80% power to detect an effect size (Cohen's d) = 0.55 for the AT analyses. In the PP analysis, assuming further 25% non-adherence in both arms among the completers (60 EXS + 30 SIS), we have 80% power to detect an effect size (Cohen's d) = 0.635. Comparable studies have found similar effect sizes.

For the analysis of bacterial families, one-way analysis of variance (ANOVA) with a Bonferroni correction to correct for multiple comparisons will be used.

F1 Unblinding Procedures

All of the research staff processing or analyzing the data will be blind to the participants' randomization until all analyses are complete.

G Data Handling and Record Keeping

G1 Confidentiality and Security

All data will be safeguarded in accordance with HIPAA and the principles and practices of strict confidentiality. Studies are done for research purposes only. The risks of breaching confidentiality will be rigorously limited by the use of locked and restricted access to data as well as numbers rather than names will be used in the database for this project. No identifiers will be included in any computer files or reports generated by this study. All key personnel involved in the design or conduct of research that involves contact with human subjects will receive the required education on the protection of human research subjects prior to funding of this project.

G2 Training

All study staff must complete CITI and HIPAA training and be listed as engaged with the IRB before they will be able to perform any study procedures. Study staff must also review protocol and sign a delegation log expressing understanding and commitment to adhere to it.

G3 Case Report Forms and Source Documents

Copies of participants' medical records containing data to be used in the study (i.e. lab values, diagnoses, lists of medication, etc.) should be placed in the file whenever possible. Should these source documents not be available, subject report is acceptable.

G4 Records Retention

Paper/hard copy records (hard copy surveys, questionnaires, case report forms, pictures, etc.) The risks of breaching confidentiality will be strictly limited by the use of locked and restricted access to data, as well as the use of participant id numbers rather than names in the data base. Hard copy research records with identifying information will be kept in a secure environment according to WUSM and HIPAA 2-lock procedure. Medical records containing PHI and research records will be maintained according to WUSM & HIPAA 2-lock policy and procedure. Only coded data will be used for data analysis and publications.

Electronic records (computer files, electronic databases, etc.) - The risks of breaching confidentiality will be strictly limited by the use of locked and restricted access to data, as well as the use of participant id numbers rather than names in the data base. No identifiers will be included in any reports generated by this study, and all sensitive electronic information containing identifiers will be kept in password-protected files on password protected computers, all in compliance with WUSM & HIPAA approved policy and practice. All imaging data will be stored on WUSM's CNDA and/or on CD's secured in the PI's or coordinator's office under the 2-lock rule. All other data will be entered and secured in the WUSM Red Cap database system. Questionnaires may be administered on paper or electronically on a secure computer. Names and identifying information of the participants completing these questionnaires will not be included in their computer file, only subject ID #s. All electronic data will be maintained in a secure database (i.e., Redcap).

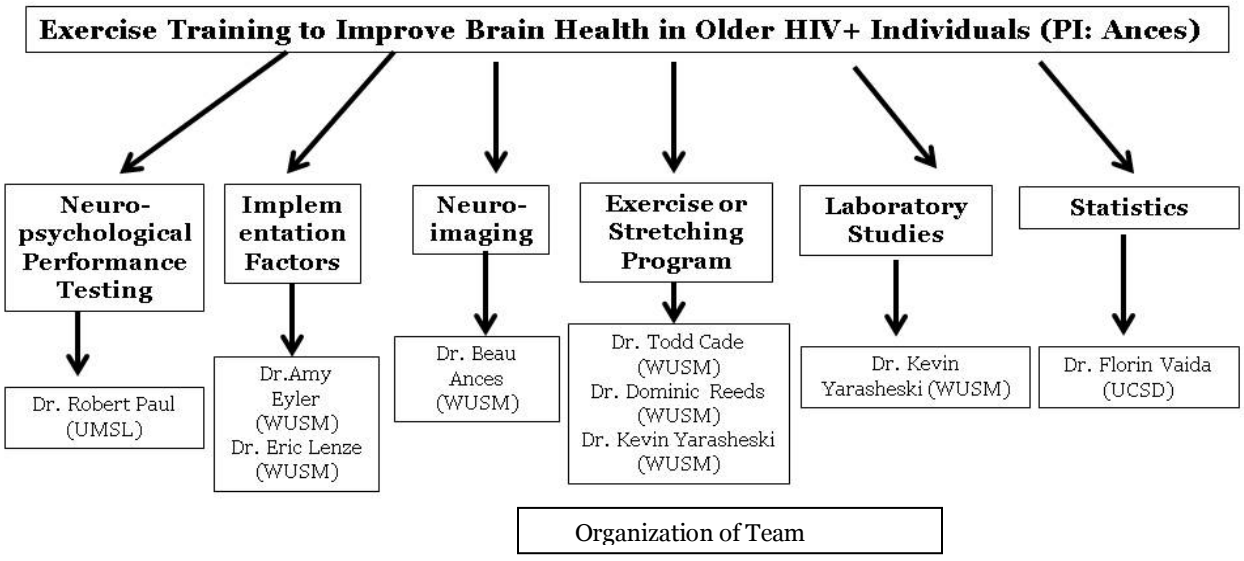
Biologic samples (blood draws, cheek swabs, saliva samples, tissue samples, etc.) - Blood will be labeled with the subject's ID code, date of draw, and time of draw. Samples will be transported by engaged study staff to the appropriate processing lab here at WUSM.

H Study Monitoring, Auditing, and Inspecting

Oversight of the study will be the responsibility of the PI and his delegates, including the study coordinator(s). Internal self-audits for quality assurance purposes will be conducted as necessary to insure study procedures are being followed and for the integrity of the data. The study will also be reviewed at least annually by HRPO/WU IRB.

I Study Administration

I1 Organization of Study Center



Organization of Team

I2 Funding Source and Conflicts of Interest

Funding is through an R01 through the National Institute of Nursing Research (NINR) at NIH.

I3 Subject Stipends or Payments

Participants will be remunerated through check or cash as noted below. Subjects' payments will be prorated based on how much of the study they complete.

BASELINE ASSESSMENTS		EXERCISE INTERVENTION	Midpoint Assessment	26 WEEK FOLLOW UP ASSESSMENTS		Remote COVID-19 Visit
Neuropsychological performance and cardio fitness	Labs and MRI	AEROBIC/RESISTANCE or STRETCHING	Mini Neuropsychological performance	Neuropsychological performance and cardio fitness	Labs and MRI	Online or phone questionnaires
$100	$50	$390 ($15 per week)	$25	$100	$50	$30

Participants will also be paid $25 for each stool sample & dietary survey they complete at baseline, 1 month, midpoint, and follow up.

I4 Study Timetable

	Year 1	Year 2	Year 3	Year 4	Year 5

Recruitment of participants			
Analysis of neurobehavioral data			
Analysis of neuropsychological data			
Analysis of neuroimaging data			
Correlation of neuroimaging and neuropsychological data			
Analysis of implementation factor data to inform dissemination of findings			

J Attachments

J1 Study procedure flow sheet

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