Protocol (including Statistical Analysis Plan)

Title: High-Intensity Exercise to Attenuate Limitations and Train Habits in Older Adults With HIV
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Hypotheses and Specific Aims:

People with HIV (PWH) aged 50 years or older now comprise a majority of the HIV epidemic in the U.S., with a life expectancy nearing that of persons without HIV. Yet even with effective antiretroviral therapy, older PWH often experience earlier development of age-associated comorbidities [1,2], poorer physical function[3-10], and a disproportionately high symptom burden[11,12]. Fatigue is one of the most common symptoms, occurring in up to 88% of PWH[13], and it is persistent[14] and disruptive to daily life[15-17]. As a multifactorial condition, fatigue can be challenging to treat, but without intervention, fatigue further contributes to poor physical function and diminished quality of life[18-20]. Scalable strategies that can preserve high physical function and mitigate fatigue are urgently needed to maximize the *healthspan* (i.e., the part of one's life in which they are in good health) of older PWH. Such interventions will 1) address the cornerstone of geriatric medicine[21] - the maintenance of physical function, 2) advance NIH's scientific priorities in HIV and aging, and 3) fulfill key population goals such as the Healthy People 2020 goal to improve quality of life and fatigue.

Across populations, regular exercise improves physical function and reduces fatigue. Most of these studies incorporate continuous moderate-intensity exercise (CME), where aerobic exercise is performed at 70%-75% of maximal heart rate (HR_{max}) continuously for a specified duration (i.e., a 30-min walk)[22]. We found that CME + moderate-intensity resistance exercise improves physical function in older PWH, with additional improvements from a higher-intensity continuous aerobic + resistance exercise program[23]. Further, only our higher-intensity (i.e., 80-90% HR_{max}) continuous aerobic + resistance intervention improved fatigue. Lastly, despite improvements in physical function and fatigue during the 6-month intervention, less than 50% of our participants continued to exercise at least once a week following the supervised intervention, demonstrating that even when exercise is beneficial it can be difficult for PWH to maintain. These data are promising, but suggest that an **innovative approach to exercise is needed to improve physical function, reduce fatigue, and maintain a self-directed exercise habit among older PWH**. Further, generalizability is limited by a small sample size, few women, and lack of different exercise types, leaving important knowledge gaps.

High-intensity interval training (HIIT) uses repeated alternating short bouts of high-intensity (e.g., 80%-95% HR_{max}) and lower intensity aerobic exercise (e.g., 60% HR_{max}). HIIT is safe and has superior efficacy in improving health outcomes compared to CME in those with chronic illness (e.g., coronary artery disease, diabetes)[24-26], yet **little is known about HIIT for PWH** [27-29]. HIIT also reduces body fat, improves muscle mass, and enhances mitochondrial bioenergetics (i.e., mitochondrial respiration rate and electron transport chain [ETC] activity), mechanisms proposed to underlie reductions in fatigue[30-32]. At both sites (University of Colorado Denver and University of Washington), participants are undergoing an optional sleep sub-study that aims to characterize the effects of two exercise interventions, HIIT and CME, on sleep and inflammation in older PWH.

Together, these data support our *overarching hypothesis:* that with the same volume of exercise**, HIIT will lead to better physical function and reduced patient-reported fatigue through improvements in mitochondrial bioenergetics compared with CME among older PWH**. We further hypothesize that older PWH randomized to HIIT will maintain self-directed exercise better than those in CME when exercise is no longer supervised, and that behavioral support will help to maintain adherence. Through a three-site (Seattle, WA, Aurora, CO, and Birmingham, AL), clinical trial comparing the clinical and bioenergetic effects of two exercise regimens that vary by interval and intensity (HIIT or CME), we will test our hypotheses through the following aims:

AIM 1. Compare the effects of two exercise regimens varying by interval and intensity on *primarily* physical function performance (i.e., 400-m walk time) and *secondarily* on patient-reported fatigue at 16-weeks. We ***hypothesize*** that PWH randomized to HIIT will experience greater improvements in physical function and reductions in fatigue compared

to CME. **Approach**: We will randomize 180 PWH (aged 50-80 years) into one of two supervised 16-week exercise interventions and compare changes in physical function and patient-reported fatigue over time.

AIM 2. Evaluate bioenergetic mechanisms underlying HIIT and CME. We ***hypothesize*** that PWH randomized to HIIT will have improved mitochondrial bioenergetics (i.e., mitochondrial respiration rate and ETC activity). **Approach**: We will evaluate 16-week changes in skeletal muscle and systemic (peripheral blood mononuclear cells [PBMCs]) mitochondrial activity among PWH in response to supervised exercise.

AIM 3. Describe and compare the effect of a biobehavioral coaching intervention to enhance self-directed exercise. **Approach**: After 16 weeks of supervised exercise, HIIT and CME participants will be randomized (in a factorial design) to a 12-week coaching intervention (vs. control) using tailored text messages to support exercise adherence. Physical activity amount (via accelerometry) and experience (via interviews) will be compared between arms using mixed analytic methods.

MUSCLE SUBSTUDY Aims:

In a mechanistic substudy at the Colorado site only, we propose to leverage the existing HEALTH infrastructure and outcomes to characterize the impact of HIIT vs CME on in vivo skeletal muscle structure and function. We will test this overarching hypothesis: Failed integration of skeletal muscle, bioenergetics, oxidative phosphorylation, and blood flow interfere with the adaptive response to exercise training in PWH, and thus limit improvements in physical function. We will investigate our hypothesis through three Aims:

Aim 1. Test the impact of 16 weeks of HIIT vs CME on myosteatosis among older PWH. Approach: Using proton density fat fraction (PDFF) magnetic resonance imaging (MRI) and skeletal muscle ultrasound (MUS) we will evaluate change in intramuscular fat with 16 weeks of HIIT or CME exercise among PWH. Hypothesis 1A. PWH will experience a decrease in myosteatosis with exercise with a greater effect in those completing HIIT than CME. Hypothesis 1B. Decreased myosteatosis will be independently associated with improved function. Hypothesis 1C. Myosteatosis will be associated with poor adaptive bioenergetic response to exercise, in vivo oxidative function and perfusion/O2 extraction.

Aim 2. Compare the effects of 16 weeks of HIIT vs CME on skeletal muscle mitochondrial function and oxidative flux among older PWH. Approach: Using ^{31}phosphorus magnetic resonance spectroscopy (31P-MRS), we will evaluate change in oxidative flux after HIIT vs CME. Hypothesis 2A: Participants in both HIIT and CME will experience an improvement in in vivo mitochondrial function, with a greater effect in the HIIT group. Hypothesis 2B: In PWH, changes in in vivo mitochondrial function with HIIT or CME will be associated with improvement in skeletal muscle mitochondrial content and oxidative capacity, and physical function.

Aim 3. Determine the relative contributions of hemodynamic and metabolic mechanisms to exercise adaptations in older PWH. Approach: Using a novel, multi-parametric MRI method (Velocity, Perfusion, Intravascular Venous Oxygenation, and T2* [vPIVOT]), we will integrate the vascular and metabolic responses to exercise among PWH. Hypothesis 3A: Vascular and metabolic adaptions to exercise will improve to a greater extent with HIIT than CME. Hypothesis 3B: In PWH, changes in microvascular blood flow and oxygen extraction with HIIT or CME will be associated with physical function improvements.

COGNITIVE SUBSTUDY AIMS

AIM 1. Compare the effects of a 4 month supervised HIIT or CME intervention on (1°) cognitive functioning (i.e., global and domain T scores and diagnoses of cognitive impairment) and (2°) subjective cognitive symptoms. We **hypothesize** that PWH randomized to HIIT will experience greater improvements in objective and subjective cognitive function compared to CME.

Exploratory Aim 1. Evaluate the biological mechanisms underlying HIIT and CME. We **hypothesize** that PWH randomized to HIIT will experience greater improvements in putative biomarkers underlying the effect of PA on cognition (blood markers: neurotrophins [e.g., BDNF], growth factors [e.g., VEGF], pro-inflammatory cytokines [e.g., IL-6] and neuroimaging markers: cerebral blood flow, resting state functional connectivity, and brain volume), which a particular focus on BDNF and cerebral blood flow, as they have demonstrated sensitivity to differences between HIIT and CME. Neuroimaging is UAB SITE ONLY.

AIM 2. Determine MoA of long-term PA maintenance at 12 months after a 4 month supervised HIIT or CME intervention AND a 3 month coaching or control texting intervention as parent of the parent study design. Distal predictors include sociodemographic (e.g., race, age, sex, education), clinical (e.g., physical health), and intervention factors (i.e., changes in parent R01 physical outcomes [cardiorespiratory fitness], condition [HIIT vs CME], [coaching vs control]). Proximal psychological MoA will be measured in real time with EMA (e.g., self-efficacy, perceived benefits, motivation, social support). We will also examine the extent to the which habitual PA in daily life impacts durability of intervention-related cognitive and biomarker improvements from AIM 1.

Impact: As older PWH experience more comorbidities and complications, nonpharmacological approaches to improve physical function and alleviate symptoms of the growing population are urgently needed. The HEALTH study will generate scientifically rigorous data on physical function and fatigue responses to exercise, the associated mitochondrial adaptations, and investigate strategies to instill sustained, self-directed exercise behavior. These data will inform the development of scalable, effective exercise recommendations tailored to the unique needs of aging PWH.

I. Background and Significance:

With advances in treatment and care, a longer life expectancy is changing the demographics of the HIV epidemic, and nearly half of those living with HIV in the U.S. are now 50 years or older. In the absence of an effective, scalable HIV cure, this population will continue to age and grow. Indeed, estimates predict that the proportion of PWH aged 50 years or older will increase to >70% by 2030[33]. PWH, even while receiving effective antiretroviral therapy (ART), have excess morbidity and mortality[34-37] compared to HIV-uninfected populations, with an earlier occurrence of aging complications including diabetes, hypertension, cardiovascular disease, osteoporosis, and fractures[1-8]. Increasing age, comorbid burden, and lifestyle factors, contribute to greater than expected impairments in key components of daily function (i.e., walking speed, balance, ability to rise from a chair)[9,10] and a high burden of symptoms including fatigue among older PWH. Older PWH urgently need biobehavioral strategies that extend their healthiest lifespan, or *healthspan*[38,39].

Physical function impairments are seen up 10 years earlier in adults aging with HIV than their uninfected peers[40-42]. Physical function is the *cornerstone* of successful aging, allowing older adults to live independently[43,44]. Yet, even with long-term, effective ART in the current era of HIV, we and others have identified impairments in physical function across several cohorts[40]. Among middle-aged PWH on effective ART in Colorado (n=359), 50% had difficulty rising from a chair 5 times[45], and that 20% met criteria for low lean mass[46]. Within the Multicenter AIDS Cohort study of men with or at risk for HIV (*n*=2025), we found that decline in gait speed was faster (0.027 m/sec/year) in PWH compared to HIV-uninfected men (p <0.001), and this difference by HIV serostatus was most apparent starting after age 50[42]. Similar differences by HIV-serostatus were seen with longitudinal changes in grip strength[41], suggesting an accelerated decline[42]. Thus, aging PWH are at high risk for accelerated development of mobility disability and muscle weakness, hallmarks of frailty. Moreover, these physical function impairments are associated with poor outcomes including an increased risk of cardiovascular disease, diabetes, bone disease, falls, hospitalizations, and mortality[47-50]. **The combination of both HIV infection and impaired physical function is associated with a greater risk of mortality than the presence of HIV or impaired function alone[51-53].** Given these consequences of impaired physical function in older PWH, promising interventions to improve function are needed.

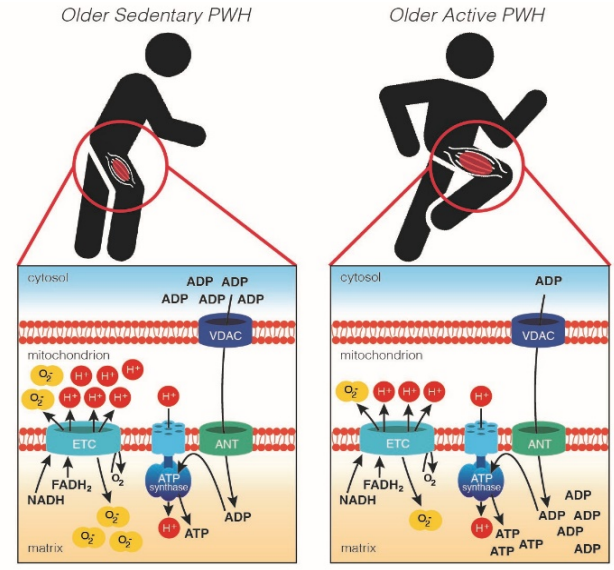
Fatigue. In addition to objective impairments in physical function, fatigue is the most common and severe *symptom* in older adults aging with HIV, [54] and occurs in up to **88% of PWH**[13,55,56]. Among 5,370 PWH seen for routine care, fatigue was the most prevalent and burdensome reported symptom (55.5%), with a higher prevalence among women (57.3%) than men (55.1%; p<0.001)[57]. In our cohort in Colorado, 45% of PWH reported moderate or severe fatigue[58]. Additionally, fatigue among PWH was more common when compared to social- and demographically- matched controls, with 25% of PWH reporting fatigue in the AgeHIV Cohort Study[59] compared to 15% of matched, HIV-uninfected adults. The etiology for the excessive prevalence of fatigue in HIV is likely multifactorial, and thus can be challenging to treat. Without intervention, fatigue further contributes to poor physical function and quality of life[18-20], in part through reduced self-efficacy to complete activities[44]. We have previously shown a strong association between physical function and fatigue assessed by the Short Form (SF)-36 in virally-suppressed PWH: every 1 m/sec slower 400-m walk time (400-MWT) predicted a 5.1 point worsening in fatigue, and every 1 rise/sec slower chair rise pace (a measure of leg strength) predicted a 13.4 point worsening in fatigue[60]. As physical function is strongly associated with fatigue, nonpharmacological interventions would ideally target both.

Greater exercise volume and intensity can improve physical function and fatigue. As we have recently reviewed[61], aerobic (endurance) or resistance exercise (RE) interventions in PWH are safe, effective and improve cardiovascular, metabolic, and functional measures in younger PWH, but little is known about older PWH[62,63]. Extrapolating from these findings, and from studies of older HIV-uninfected persons, the Department of Health and Human Services (DHHS) Physical Activity (PA) guidelines can be generally recommended for older PWH (i.e., 150-300 minutes of moderate-intensity or 75-150 minutes of vigorous aerobic PA), including RE at least twice weekly[64-66]. Using these recommendations[67], we designed the Exercise for Healthy Aging Study to test the effects of continuous aerobic exercise and RE at two intensity levels among 69 older adults (50-75 years) with or without HIV infection[23]. All participants began with 12 weeks of CME and moderate-intensity RE, and then were randomized to continue moderate or advance to high-intensity exercise for 12 additional weeks. We found significant improvements in physical function regardless of intensity (see preliminary data, Fig 2.), with greater gains in muscle strength and reduction in fatigue (SF36) among PWH randomized to high intensity exercise. Furthermore, in a cross-sectional study examining relationships among self-reported PA, fatigue, and quality of life in 90 PWH, we found that those who engaged in at least 150 minutes of moderate-intensity PA (e.g., walking) per week had a clinically-meaningful (17%) reduction in fatigue[68]. This work supports our *scientific premise* that higher intensity exercise will lead to better physical function and reduced patient-reported fatigue, compared to moderate intensity exercise in older PWH.

High Intensity Interval Training (HIIT). HIIT refers to repeated short bouts of high-intensity aerobic exercise (80%-95% HR_{max}) alternated with shorter lower-intensity recovery bouts. The current DHHS PA Guidelines acknowledge that HIIT may impart greater cardiovascular benefits than CME in adults with increased cardiovascular disease risk factors[25,69]. Among adults with chronic disease-related fatigue or frailty, supervised HIIT appears as safe and may be more effective at improving functional measures than low or moderate-intensity interventions[70,71]. Compared to CME, HIIT was associated with greater improvements in mobility in older adults with knee osteoarthritis[72]. In breast cancer survivors and patients with psoriatic arthritis[73-75], HIIT was associated with reduced fatigue compared to usual care. Although detractors have suggested that HIIT may be intimidating to sedentary adults, this was not the case in Onley et. al.[76] who reported that sedentary adults who underwent HIIT found it equally enjoyable as a single bout of CME. Indeed, in sedentary older adults with diabetes, HIIT training was well-tolerated while CME was perceived to be boring[77]; among 100 overweight women, 42% self-selected HIIT over CME[78].

The effects of HIIT on physical function in older PWH have not been studied. Evaluation of high-intensity exercise in PWH may be important, as this population appears to have greater impairment in cardiorespiratory capacity (i.e., peak oxygen consumption, VO_{2peak}) compared to age-matched HIV-uninfected controls[79], with even greater impairments among older PWH with non-AIDS comorbidities[80]. Impaired peripheral oxygen uptake[81], cardiac response to exercise[82], or oxygen diffusion capacity[83] related to HIV or exposure to older ART, suggest that PWH may require a different exercise dose to restore and achieve levels of cardiovascular fitness and physical function similar to HIV-uninfected peers. Conversely, these impairments may make exercise more difficult in older PWH, thus undermining their self-efficacy to maintain long-term exercise adherence. But we do not know the answer to these important clinical questions. The 2018 DHHS PA guidelines do not provide specific recommendations for PWH because the evidence base is too scant[84]. *To better inform the dose of exercise needed for maximal benefit in older PWH, we will compare changes in their physical function and fatigue in response to two levels of exercise intensity.*

Figure 1. *Hypothesized skeletal muscle mitochondrial adaptations in response to exercise where mitochondrial respiration is more enhanced in response to HIIT (adapted from Holloway et al, 2018)*



Mitochondrial Adaptations. Among the plausible biological mechanisms underpinning the functional improvements with HIIT, is enhanced mitochondrial function (Figure 1). Mitochondrial activity is directly influenced by the quantity of mitochondrial proteins as determined by the cell's DNA[85]. Yet, as individuals age, there is a decline in mitochondrial DNA and activity. Older age is associated with lower skeletal muscle total mitochondrial DNA mitochondrial mass[86], enzyme activity (i.e., citrate synthase, cytochrome oxidase)[87], and mitochondrial respiration (Complex I+ II) in HIV-uninfected adults[85]. Lower muscle mitochondrial content and impaired activity were

associated with older age, lower VO_{2peak}, and slower walk speed[86,88]. A physically active lifestyle during older age may preserve mitochondrial function to levels seen in young adults[85,87].

Several lines of evidence suggest that mitochondrial bioenergetics (i.e., mitochondrial respiration rate and electron transport chain (ETC) activity) can be better enhanced with HIIT compared to CME. In young men, muscle mitochondrial respiration and activity of citrate synthase and ETC (CI, CI+II) increased more in response to HIIT than CME, despite a volume-matched workload[89]. In patients with heart failure (aged 60 years), platelet ETC activity increased significantly with HIIT but not CME training (12 weeks), and the changes in VO_{2peak} and ETC activity were positively correlated[90]. Most convincingly, HIIT increased maximal muscle mitochondrial respiration more strongly in healthy older than young adults (69% v. 49%), but lower intensity exercise (akin to CME) had no effect on mitochondrial respiration in older adults[85]. Encouragingly, among 7 PWH mitochondrial respiration in peripheral blood mononuclear cells (PBMCs) increased 2.45-fold with CME, further indicating a need for well-powered RCTs comparing HIIT to CME in this population[91].

The association of fatigue with mitochondrial function (other than in mitochondrial diseases) is not well-established. In men with non-metastatic prostate cancer[92], patient-reported fatigue increased and Complex III oxidation in PBMCs decreased during radiation therapy. In older adults with idiopathic chronic fatigue, markers of mitochondrial bioenergetics (i.e., peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1a) and cytochrome IV and V expression) in muscle was lower than in age-matched controls[93], whereas self-reported fatigue (SF-36) was not associated with PBMC mitochondrial respiration in older adults[94]. Whether mitochondrial bioenergetics are associated with fatigue in older PWH has yet to be determined.

Innovative approaches to improve long-term exercise adherence are needed: we propose HIIT and behavioral coaching. ***First***, as HIIT has more inherent variety, it may lead to better long-term exercise adherence with less "boredom" (one of the most common reasons cited for discontinuing exercise) and greater enjoyment than CME[95]. Existing literature supports this hypothesis: (1) Participants randomized to HIIT reported greater enjoyment than those randomized to CME[78]; (2) High intensity circuit training increased motivation to exercise to a greater extent than CME, despite a lower perceived exertion with CME[96]; and (3) HIIT is associated with >20% higher adherence than CME[97]. In a scoping review, participants preferred HIIT over CME in 5 of 6 studies, with no clear preference for HIIT or CME in the 6th [98]. Given this evidence, we believe that PWH randomized to HIIT will have better long-term exercise adherence compared to PWH participating in CME. With the potential *substantial* benefits of long-term HIIT on physical function, fatigue, and ultimately the quality of life of older PWH, the short and long-term effects of HIIT and CME need to be examined. ***Second,*** coupling an exercise intervention with a theoretically-based coaching intervention is likely to enhance long-term adherence to exercise. Adherence to exercise is hard for any population, but for older PWH it may be especially challenging[84,99,100], and few evidence-based adherence strategies exist. Increasing self-efficacy for a healthy behavior may improve longer-term adherence[101]. Kekäläinen et al. reported that among older (65-75 years), sedentary, community-dwelling adults who had recently completed a 9-month supervised exercise intervention, those maintaining self-directed exercise at one year had increases in self-efficacy and intrinsic motivation[102]. Motivation has also been found to enhance medication adherence among PWH and can be modified by interventions, such as the coaching proposed in this study[103]. By examining how supervised HIIT or CME (likely to improve exercise self-efficacy) and a tailored behavioral coaching intervention (likely to improve exercise motivation) synergize to affect long-term exercise adherence in older PWH, our study is likely to generate important novel data that will enhance the healthspan of this, and other vulnerable, populations.

Table 1: Justification for the Scientific Premise of the HEALTH Study

Scientific Premise: HIIT will lead to better physical function and reduced patient-reported fatigue, compared with CME in older PWH.

Existing Support for the Premise	How This Study Extends the Evidence
Exercise is associated with improved physical function & reduced symptoms in PWH.	Well-powered, prospective, rigorous, experimental data will definitively answer this question and provide evidence of differential response by sex or other characteristics.
HIIT leads to greater physiological improvements vs CME in HIV-uninfected populations with chronic disease.	HIV-specific data accounting for HIV-associated impairments in physical function, fatigue, & mitochondrial activity.

HIIT improves adherence to regular physical activity/exercise.	Behavioral support for self-directed exercise following supervised exercise will address maintenance of exercise in PWH.

Overall significance of knowledge to be gained (Table 1): As detailed above, even with effective ART, aging PWH experience impairments in physical function and disabling fatigue at higher rates than their peers without HIV. These impairments can further limit activity and contribute to a vicious downward spiral. One of the only interventions we can offer to preserve physical function and decrease fatigue is regular exercise, however older PWH face barriers to initiating and maintaining exercise, and may not have the same bioenergetic response to the exercise stimulus, limiting the physiologic response. HIIT is an innovative approach to exercise that may overcome some of these barriers, and has been shown safe, effective, and desirable to older adults with comorbidities. This investigation into the potential superior benefits of HIIT will provide patients and providers with evidence on the most effective exercise and behavioral interventions to extend *healthspan,* in the face of many comorbid conditions often experienced by older PWH.

Our application includes several innovative features responsive to the National Institute of Aging's goal of improving the health, well-being and independence of adults as they age. **First,** our findings will advance the interdependent science of aging by describing the clinical, biochemical, and physiological effects of HIIT compared to CME on physical function and fatigue. Such data in any older population are almost non-existent. We will contribute to existing knowledge by testing these exercise regimens in a chronically-ill, heavily-fatigued population (PWH). **Second**, despite the well-recognized effects of HIIT and CME on mitochondria, little is known about the effect of these interventions on mitochondria in PWH (with existing impairments in function) and far less in women living with HIV. *This is particularly novel because, age, HIV, and even modern ART appear to have deleterious effects on mitochondrial activity*[104,105]. The HEALTH study is designed to address this gap and generate new knowledge on the local (skeletal muscle) and systemic (PBMCs) mitochondrial effects. We will enroll sufficient number of women (*n*=25) to describe sex effects. **Third**, with 25% women, we will be uniquely poised to examine sex-specific responses to exercise intensity, including changes in physical function, fatigue, bioenergetics, and exercise adherence. **Fourth**, previous studies examining how to sustain exercise in PWH have either been cross-sectional or used single methods. Our integration of longitudinal quantitative (i.e., accelerometry) and qualitative (i.e., interview) methods, coupled with our detailed mixed methods analysis (see below), will better illuminate how to sustain the habit of exercise in this population. **Fifth**, previous exercise interventions in PWH are single-site, limiting generalizability. By harnessing the experience and infrastructure of two diverse sites, we will create high-quality, reproducible data that can be generalized to the larger population of older PWH living in the U.S. **Sixth**, this study uniquely incorporates an exercise adherence component to help support long-term sustainability and maintenance of the exercise habit. By systematically studying the long-term adherence of HIIT and CME, we will advance behavioral science in this area thus allowing us to develop and disseminate strategies to improve the long-term health status of older adults in diverse populations.

II. Preliminary Studies/Progress Report:

Exercise Improves Physical Function. In our exercise intervention of 69 older adults (32 PWH), we observed significant improvements in physical function on nearly all physical function measures, regardless of serostatus (Figure 2a) [23]. Compared to HIV-uninfected participants, PWH had significantly greater percent improvements in VO_{2peak} (endurance) between weeks 0-12, and greater percent improvement in 400-MWT and stair climb between weeks 13-24. When we compared changes in physical function by exercise intensity (Figure 2b), as indicated with the pink bars, PWH randomized to higher intensity continuous aerobic + resistance experienced *greater* gains in strength, with a trend towards greater improvement in 400-MWT.

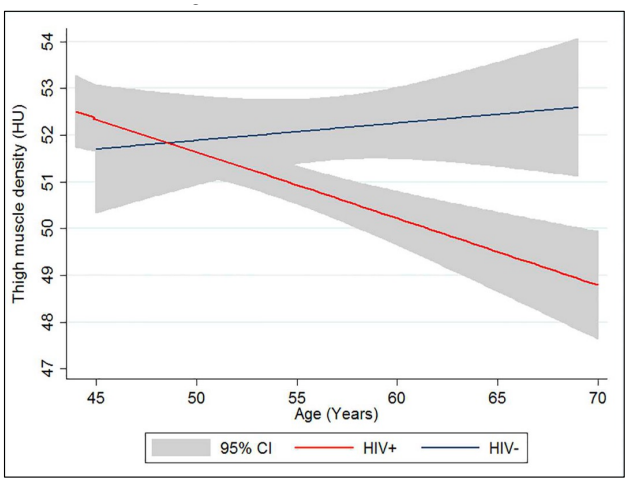
PWH recognized additional exercise benefits beyond objective assessments, described in focus groups[106]: "The thing about exercise is as soon as you start doing it, you start feeling good" and "In a very short period of time you can go from being a couch potato, from being a blob, to feeling good…your mood changes and you start to feel like, my god, I'm happier." Decreased fatigue was readily apparent: "Well, running up and down the stairs after dogs and being on my feet for 5 hours straight. That's fantastic. I mean, normally it was like find me a chair. *Now I have more energy*".

Greater quantity or intensity of PA is associated with less fatigue in PWH. In a study of 109 PWH (mean age 53 years), we found that, after controlling for age and gender, greater cardiorespiratory fitness (of which exercise is a primary driver[107]) was associated with lower levels of fatigue (ß= -0.163; p<=0.01)[108]. To determine if the inverse associations between PA and fatigue held across populations we conducted the largest study of symptoms in PWH to date[109]. In 5,370 PWH, fatigue was the most frequent (reported by 56%) and burdensome symptom. After adjusting for demographic and

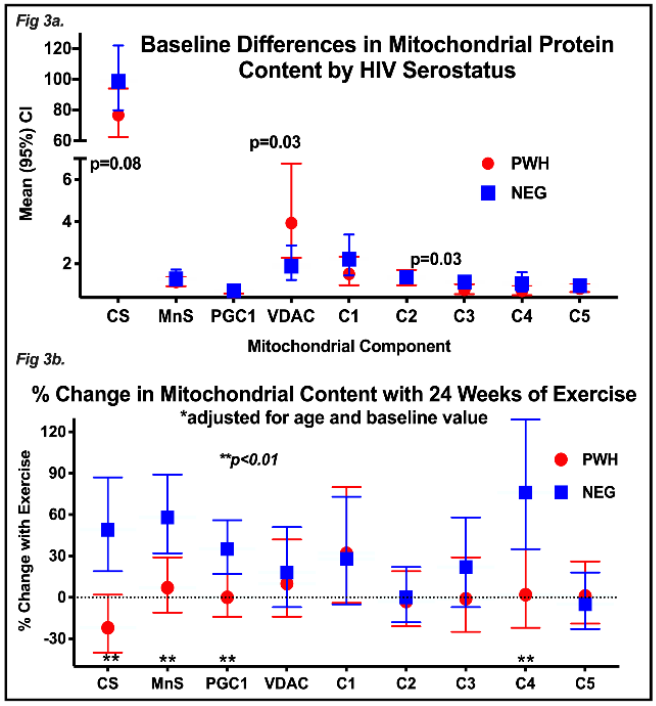
HIV characteristics, higher intensity PA was associated with lower fatigue. Specifically, sedentary participants were almost twice as likely to experience more burdensome fatigue compared to those who engaged in moderate-intensity PA (OR 2.2 [95% CI 1.9, 2.6]), and almost five times as likely when compared to those who engaged in higher-intensity PA (OR 4.7 [95% CI 3.9, 5.6])[109]. Lastly, in our exercise intervention[23], we found that baseline fatigues scores were 12.5 points worse in PWH compared to uninfected participants. Improvements in fatigue were significantly *greater* among participants randomized to high vs moderate-intensity exercise (3.9 [1.1, 6.6] vs -1.4 [-3.1, 0.2; *p*=0.002).

Mitochondrial dysfunction (induced by age, HIV, and even contemporary ART) may underlie physical function impairments and fatigue in PWH. Skeletal muscle mitochondria of men with HIV on ART (including more mitochondrial toxic therapy such as zidovudine) had 17% lower ATP content and reduced oxidative enzyme activity (i.e., citrate synthase and *β*-HAD activity) compared to uninfected controls[110]. Moreover, oxidative enzyme activity was directly related to aerobic capacity (VO_{2peak})[110], suggesting that greater skeletal muscle mitochondrial impairment underlies poorer aerobic fitness among PWH, despite effective ART. **We obtained *vastus lateralis* skeletal muscle biopsies before and after our 24-week exercise intervention.** At baseline (Figure 3), slower 400-MWT was associated with mitochondrial components: lower citrate synthase activity (CS; *p*=0.07); cytochrome complex 1 (*p*=0.03), 3 (*p*=0.08), and 4 (*p*=0.001); manganese superoxide dismutase (MnS, *p*=0.03) expression; and greater voltage dependent anion channel expression (VDAC; a mitochondrial protein regulating exchange of ions between the mitochondria and cytosol, *p*=0.03).

<u>Age-related loss of skeletal muscle quality and quantity are significant contributors to functional decline.</u> Declines in both muscle quantity (mass) and quality (degree of fatty infiltration) begin in the 3rd or 4th decade of life. With aging, PWH experience greater than expected declines in lean mass (a proxy for skeletal muscle mass)[22,23], which has been closely linked with poorer physical function[24-26]. Furthermore, PWH appear to experience greater declines in muscle quality with increasing age, compared to HIV-uninfected controls (**Fig 2**). The *quality* of the muscle may provide a similar or better estimate of subsequent complications than muscle quantity[27]. Multiple large cohort studies of older adults without HIV have shown strong associations between lower quality (i.e., fattier or less dense) muscle and poor physical function[28], hospitalizations[27], falls[29,30], and fracture[31]. Exercise is an effective intervention to improve both muscle quantity and quality among older adults. We have previously shown gains in muscle *quantity* in the setting of supervised exercise, although attenuated among PWH[32]. Whether PWH experience similar improvements in muscle *quality* with exercise, and whether these changes are directly related to improvement in physical function, are unknown.



Exercise Does Not Completely Restore Mitochondrial Function. In our exercise participants[23], at baseline (*n*=40; 18 PWH), PWH had lower CS activity and greater VDAC (Fig 3a). Compared to controls, the mitochondrial adaptations to exercise training (*n*= 31; 15 PWH) at moderate or high intensity were blunted in PWH as evidenced by significantly smaller increases in CS activity and protein expression of MnS, PGC-1α, and cytochrome complex (C4) (Fig 3b). Sample size precluded further analysis of an exercise intensity effect on mitochondrial respiration rate and electron transport activity. *However, these preliminary findings suggest that a stronger exercise stimulus (e.g., HIIT) may be necessary to stimulate mitochondrial adaptations in older PWH compared to older uninfected adults*.



In combination, these data suggest differences in the skeletal muscle and metabolic adaptations among PWH, both at baseline and in response to exercise training. *Whether these responses are due to impairment in the muscle itself, impairment in skeletal muscle oxygen extraction and utilization, or impaired muscle substrate delivery is difficult to discern, but could have a major clinical impact on targeted interventions to preserve muscle function among PWH.*

In addition to physical function limitations, impairments in *aerobic capacity* have been reported among asymptomatic PWH as young as late adolescence[35,36] and into older age[37]. Peak oxygen consumption (peak VO_2) obtained by graded exercise testing characterizes the whole body response to exercise. Multiple factors may impact aerobic capacity including impaired oxygen delivery to tissue, impaired oxygen uptake at the tissue level, or an uncoupling of blood flow versus metabolism. In the general population, limitations in aerobic capacity are consistently associated with premature mortality[38]. Prior studies of PWH in the early years of ART suggest that even well-suppressed PWH may have impaired peripheral tissue oxygen extraction or utilization despite obtaining peak VO_2[39,40]. However, participants in these studies were relatively young (age 30s-40s) with a shorter duration of ART (mean 40-45 months)[39]. Increasing age and duration of ART and HIV may have different effects among people aging with HIV in the current treatment era.

Insufficient *substrate delivery* to muscle tissue may also contribute to impaired exercise capacity in PWH, as a result of decreased cardiac output, peripheral artery disease, or microvascular impairment at the level of the tissue. Indeed, increasing age and ongoing inflammation contribute to a markedly higher risk of cardiovascular disease among PWH[41]; peripheral artery disease also occurs more frequently among PWH than uninfected controls[41-43]. Increasing evidence also implicates microvascular dysfunction in the pathogenesis of both coronary and peripheral vascular disease risk in PWH, as a consequence of chronic inflammation and immune activation[44]. Among older adults with HIV, cardiovascular disease is strongly associated with impaired physical function and frailty[19,45,46]. Although less is known about the functional implications of peripheral artery disease and microvascular disease among older PWH, the implications in other populations are apparent: among older asymptomatic adults without HIV, lower ankle-brachial indices (indicating impaired blood blow) were strongly associated with slower 400-m walk time (MWT)[47]. Members of our team have consistently found that microvascular disease is a major determinant of impaired exercise tolerance in other populations without HIV[48-50].

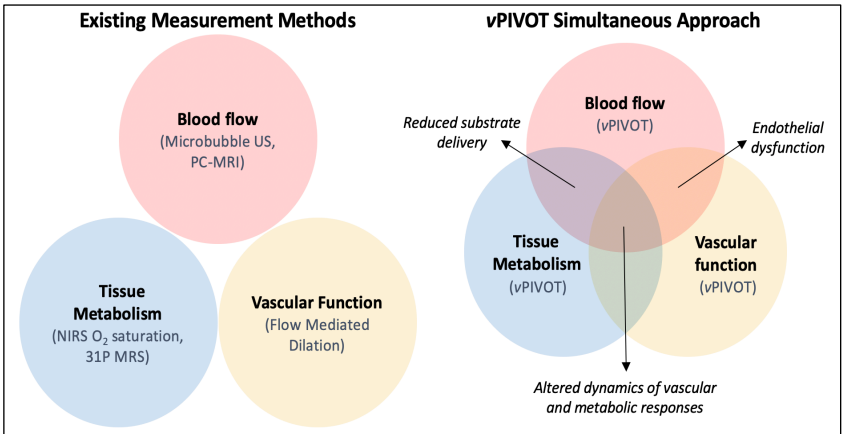


Figure 4. Conventional methods measure single, isolated parameters, rendering them incapable of assessing the interdependent physiologic processes. *v*PIVOT's simultaneous, interleaved approach provides a comprehensive hemodynamic and metabolic tool to measure the individual, *as well as coordinated* processes.

Existing methods to probe the underlying mechanisms of exercise intolerance are only capable of evaluating a single component of the vascular or metabolic response (**Fig 4**). For example, vascular function has been assessed by measuring blood flow changes evoked by a vasoactive stimulus (e.g. exercise, induced ischemia) in the large artery or at the tissue-level [51-56]. However, by measuring macro-vascular and microvascular systems in isolation, it is impossible to resolve the contribution of resistance arteries versus capillaries on the measured vascular reactivity. Additionally, these flow responses on their own do not account for differences in underlying metabolic mediators. Measures of mitochondrial physiology (e.g., Oroboros) test function in an ideal state with adequate substrate. ^{31}P-magnetic resonance spectroscopy (MRS) can provide an *in vivo* measure of metabolism in skeletal muscle but, ^{31}P-MRS is non-localized and the measurement of oxidative capacity cannot differentiate between reduced substrate delivery versus mitochondrial dysfunction. **To develop a comprehensive mechanistic understanding of muscle's response to exercise among PWH, the simultaneous contributions of blood flow, oxygen extraction, and oxidative metabolism must all be resolved.**

The health benefits of an exercise intervention would be more meaningful if exercise was maintained thereafter. Despite high exercise adherence (92%) during our intervention, most of our participants returned to their pre-intervention sedentary habits. Indeed, <50% reported exercising ≥1 day/week at 12 weeks post-intervention. The marked gains in physical function and exercise self-efficacy (>70% felt "a lot more confident in my ability to exercise") did not carry over to self-directed exercise. These findings clearly point to a need for *innovative interventions incorporating behavior change strategies.* Regular PA over the lifespan is critical to the health of our nation, particularly among those with multiple chronic health conditions, such as adults aging with HIV. A number of qualitative studies, including our own, have explored attitudes towards PA among diverse PWH and have identified several influencing factors, such as comorbidities, self-efficacy, social support, and accessibility of safe environments for exercise[19-24]. In focus groups of older PWH in Colorado, participants shared barriers to routine PA, including a lack of social support, loneliness, low exercise self-efficacy (i.e., not sure what to do), and a negative perception of the gym culture. Every group had unprompted discussion about social isolation, or loss of friends or partners due to HIV or other causes, threatening the important social support motivator for exercise. **Many common and unique barriers limit uptake of exercise behaviors among older PWH; empowering this population with tools to overcome these barriers is essential to creating sustainable PA interventions.**

In summary, our preliminary data suggest a strong relationship between PA, physical function, and fatigue with greater benefits seen with higher intensity activity. Based on data from our prior exercise intervention, we anticipate that higher intensity exercise (e.g., HIIT) is likely to lead to greater improvements in physical function and reductions in patient-reported fatigue (**Aim 1**) compared to CME. We further hypothesize greater changes in mitochondrial bioenergetics with HIIT, and that these changes will be related to improved physical function and fatigue (**Aim 2**). We expect that HIIT will result in greater exercise satisfaction and likelihood of long-term continuation of exercise (**Aim 3**). Using a coaching intervention for self-directed exercise that combines motivational interviewing and personalized support during the maintenance phase (Aim 3), we seek to develop the ideal "cocktail" to promote healthspan among older PWH in the current era of ART.

IV. Research Methods

A. Outcome Measure(s):

Primary Outcome Measures

1. Change in 400-meter walk test (MWT) from week 0-16.

Secondary Outcome Measures

1. Change in Lee Fatigue Scale (*LFS)* from week 0-16.
2. Change in 400-MWT from week 0-28.
3. Change in *LFS* from week 0-28.
4. Change in state 3 respiration (from skeletal muscle) from week 0-16.
5. Change in state 3 respiration (from PBMCs) from week 0-16.
6. Total Actigraphy-measured time spent in physical activity per week and daily step count from week 17-28.
7. Perception of physical activity (qualitative interviews) at weeks 0, 16, 28.

Exploratory Outcome Measures

1. Change in 1-RM adjusted for lean body mass from week 0-16.
2. Change in VO_2 maximum from week 0-16.
3. Change in Short Performance Physical Battery (SPPB) and modified SPPB from week 0-16 and 0-28

4. Change in PROMIS-measured fatigue from week 0-16 and 0-28.
5. Change in DXA-measured total body fat and lean body mass from week 0-16.
6. Change in electron transport chain activity (skeletal muscle) from week 0-16.
7. Change in electron transport chain activity (PBMCs) from week 0-16.
8. Change in mitochondrial content (skeletal muscle) from week 0-16.
9. Change in mitochondrial content (PBMC) from week 0-16.
10. Change in physical function outcomes, patient-fatigue and physical activity adherence from week 17-28 by exercise and coaching intervention.
11. Change in mitochondrial bioenergetics, physical function and fatigue at baseline, week 16, and change from 0-16
12. Change in self-reported 3 day diet intake from week 0-16.
13. Change in stool microbiome and short-chain fatty acids from week 0-16
14. Change in muscle fat by proton density fat fraction (PDFF), intramyocellular lipid (IMCL) and extramyocellular lipid (EMCL) from week 0-16
15. Change in oxidative phosphorylation (OxPhos) from week 0-16.
16. Change in mean VO_2 response *in the gastrocnemius and soleus muscles* from week 0-16.
17. Change in lean muscle quality and quantity from week 0-16 by muscle ultrasound.
18. Explore the barriers and facilitators for non-participation in an exercise-related clinical trial.
19. Change in cognitive functioning (i.e., global and domain T scores) and subjective cognitive symptoms (self-report questionnaires) from 0 to 48 weeks.
20. Change in blood markers (neurotrophins [e.g., BDNF], growth factors [e.g., VEGF], pro-inflammatory cytokines [e.g., IL-6]) from 0 to 48 weeks
21. Change in neuroimaging markers: cerebral blood flow, resting state functional connectivity, and brain volume), from 0 to 16 weeks (UAB SITE ONLY)
22. Psychological mechanisms of adherence to exercise at 48 weeks (measured with questionnaires and text message surveys)

B. Description of Population to be Enrolled:

	Consented	Begin Intervention	Number of women	Complete Intervention
Colorado	Up to 100	N=60	Goal 25%	N=50
Seattle/UW	Up to 100	N=60	Goal 25%	N=50
UAB	Up to 100	N=60	Goal 25%	N=50

This study will involve the recruitment and retention of men and women (*n*=180) at three sites (n=60 each site) with HIV infection who are stable on HIV antiretroviral therapy. Study volunteers must meet general criteria to be eligible for further screening for participation in the study. In most cases, this information will be acquired during a telephone interview prior to a screening/consent visit. *The inclusion and exclusion criteria have been carefully selected to enroll the most appropriate study population while also protecting the generalizability of the findings. A*ll participants will engage in a 16-week randomized exercise intervention (high-intensity interval training [HIIT] vs continuous moderate exercise [CME], followed by a 12-week exercise maintenance intervention in which participants are also randomized to a coaching vs control intervention. Up to 40 participants will be given the opportunity to co-enroll in a qualitative substudy (Aim 3) where they will participate in three one-on-one interviews (at weeks 0,16,28) to capture perspectives on sustaining a self-directed exercise habit. Up to 40 participants (Colorado and Washinton only) will be given the opportunity to participate in an MRI/MRS substudy with imaging at baseline and week 16. Up to 20 participants (Colorado, Washinton, and Alabama) will be given the opportunity to complete the 16 week exercise intervention at a recreational center. The total study duration will be 28 weeks at UCD and UW with the option to enroll in a 12 month follow up (48 weeks). The total study duration will be 48 weeks at UAB.

<u>*Characteristics of the Population*</u>*:* Potential participants will be recruited from HIV specialty clinics at our sites. Adults living with HIV will be included if they meet the following eligibility criteria:

Inclusion criteria*:*

- **Aged ≥ 50years**,
- **Sedentary lifestyle,** defined by self-reported physical activity that breaks a sweat <3 days/week, with no regular resistance exercise for 3 months preceding study,
- **Fatigued** (≥2.0 on either of the first two screening items on the *HIV-Related Fatigue Scale*), [1, 2]

- **Thyroid Stimulating Hormone (TSH)** within normal lab limits,
- **Prescribed HIV antiretroviral therapy** for ≥ 12 months, with no current use (within 1 year) of older drugs with established mitochondrial toxicity (i.e., D4T, DDI, ZDV),
- **HIV-1 RNA level < 200 copies/mL**, for a minimum of 12 months prior to enrollment, with an allowed blip to 500 copies/mL presuming repeat assessments are below 200 copies,
- **Willing to participate** in either assigned arm of a 16-week supervised exercise intervention 3 times weekly,
- **Ability to receive messages** from cell phone or email in order to participate in the biobehavioral maintenance intervention,
- **Ability and willingness of participant to provide informed consent** and consent for access to medical record,
- **Completed COVID-19 vaccination and appropriate COVID-19 boosters**

These inclusion criteria are designed to identify a representative group of older adults living with HIV who experience a variety of physical function limitations and symptoms and may benefit from our proposed intervention. Participants are not eligible if the meet any *exclusion criteria*:

Exclusion criteria:

- **Weight over 450 pounds** (due to limitations of the DXA machine)
- **Use of sex hormone therapy,** if on for ≤3 months (stable doses for >3 months will be permitted)
- **Use of other hormone replacement,** if on for ≤ 3 months (stable doses >3 months will be permitted)
- **Anemia** (Hemoglobin ≤9 g/dL for women or ≤10 g/dL for men) due to contribution to fatigue,
- Diagnosis of **mitochondrial disease**,
- For participants undergoing the muscle biopsy only, use of anticoagulant therapy other than low dose aspirin that cannot be held for at least 7 days for the muscle biopsy. Aspirin and non-steroidal use will be permitted but will be held for 7 days prior to the muscle biopsy, and can be resumed following the biopsy.
- For the MRI/MRS optional imaging: participants with implanted devices (i.e. pacemaker or insulin pumps), have severe claustrophobia, and females who are pregnant will be excluded.
- Due to the expected fatigue associated with COVID-19 and potential infection risk, anyone with a diagnosis of COVID will not be eligible for enrollment until at least 30 days after symptom resolution and return to baseline level of function.
- **Active substance abuse** or other factors that could prevent compliance or safety with study visits, at the discretion of the site investigator,
- Reasons for **medical exclusion**, as determined by Dr. Erlandson or a provider at the University of Washington:
    - **Uncontrolled hypertension** defined as resting systolic blood pressure >150 mmHg or diastolic blood pressure >90 mmHg; participants who do not meet these criteria at first screening will be re-evaluated, including follow-up evaluation by their primary care provider with initiation or adjustment of anti-hypertensive medications,
    - **Unstable ischemic heart disease** (e.g., angina, ST segment depression) or **serious arrhythmias** at rest or during the graded exercise test without negative follow-up evaluation will be cause for exclusion; follow-up evaluation must include diagnostic testing (e.g., thallium stress test) with interpretation by a cardiologist,
    - **New York Heart Association Class III or IV congestive heart failure**, clinically significant aortic stenosis, uncontrolled angina, or uncontrolled arrhythmia,
    - **Pulmonary disease** requiring the use of supplemental oxygen at rest or with physical exertion,
    - **Malignancy** requiring chemotherapy or radiation therapy within 24 weeks prior to enrollment,
    - **Poorly controlled diabetes**, as evidenced by hemoglobin A1c > 8.0, documented within 6 months of study visit,
    - **Surgery/trauma/injury/fracture** within 24 weeks prior to enrollment that, in the opinion of the study physician, may impact a subject's baseline functional testing and ability to exercise,
    - **Balance impairments** that may impact functional testing and ability to safely exercise as reported by the participant or in their medical record,
    - **Orthopedic problems** (e.g., severe osteoarthritis, rheumatoid arthritis) that greatly limit the ability to perform moderate intensity resistance exercise (e.g., unable to be properly positioned in exercise equipment or to have severely restricted range of motion even after modifications have been made),
    - Persons who, in the judgment of the study physician, appear to have **unstable health** or are **incapable of safely participating** in the exercise intervention.

In 2019, we estimate that at least 500 older adults living with HIV in care at the two clinical sites would meet our inclusion criteria and would be eligible for enrollment. If we have trouble recruiting, we have access to additional community sites associated with our academic medical centers with similar demographics.

*optional; Full physical function = SPPB, mSPPB, frailty, 400-mwt. Brief physical function = 400-mwt and 10x chair rise only

Involvement of special vulnerable populations.
Minority populations will be enrolled. While this group is considered a vulnerable population, the study team has considerable experience enrolling these participants. Given the increased prevalence of physical function limitations and fatigue in these populations, it is important that they are not excluded from participation in this study.

C. Study Design and Research Methods

Aim 1. Compare the effects of HIIT and CME on physical function (1°) and fatigue (2°) in older PWH.

Procedures/Outcome Measures (Table 3)

	Baseline (up to 8 weeks)				Week of HIIT vs CME (Aim 1)					End of Part 1 Visit (can overlap with week 16 visits) Coach vs Control		(Aim 3)				End of Primary Study	End of Cognitive Substudy
	#1	#2	#3	#4	0	2	4	8	12	16		0	4	8	12	28	48
Consent	X																
Medical History	X																
Physical exam	X																
VO_2 peak	X									(or X)	X (not on same day of physical function or muscle biopsy)						
MRI Scan				X							X						
Urine Pregnancy Test (if menstruating)			X (prior to DXA scan)							X (prior to DXA scan)							
DXA			X							(or X)	X (ideally before V02)						
1-RM						X	X	X	X								
Physical Function (FULL)			X							X						X	
Physical function (BRIEF)					X		X	X	X				X	X	X		
Fatigue			X		X		X	X	X	X			X	X	X	X	
Questionnaires			X		X					X						X	X
Health Status					X		X	X	X	X			X	X	X	X	
Randomization			X								X						
Blood draw		X									X (same day as, prior to biopsy)						X
Muscle biopsy*		X									X (≥48 hours after V02)						
Muscle ultrasound*			X							X							
Mitochondrial assays		X									X						

Actigraphy		Receive	Return							Receive	Return		X	X	X	X	X
Stool collection*		Receive	Return							Receive	Return						
Microbiome Questionnaire (Collect with stool)		Receive	Return							Receive	Return						
Ultrasound Feasibility Questionnaire (collect during 2nd US visit)										X							
Connor Davidson Resilience Scale			X							X							X
Diet log		Receive	Return							Receive	Return						
Cognitive assessment[CS]		X	X		X					X						X	X
Adherence Text Message Surveys																	X
Interviews *			X								X					X	X
HIIT vs CME					X		X	X	X	X							
Coach vs Control												X	X	X	X		
Note. CS=Optional if participants opt in for Cognitive Substudy, tentative on the visit performed, pending other optional tests and participant preference																	

STUDY MEASURES BY SITE		
	UW/UCD	**UAB**
4 mo. HIIT vs CME Intervention	**X**	**X**
3 mo. coaching texting Intervention	**X**	**X**
VO_2	**X**	**X**
DXA	**X**	

Actigraphy	**X**	
Blood Draw	**X**	**X**
Physical Function and Fatigue	**X**	**X**
Cognitive Testing	**X**	**X**
Neuro-imaging		**X**
Muscle-imaging	**X**	
Muscle biopsy	**X**	
Stool Sample	**X**	
Sleep Study Measures	**X**	
Surveys	**X**	**X**
Qualitative Interviews	**X**	**X**
Note. Cognitive substudy measures are optional for UCD/UW participants. Neuroimaging is UAB only, but only for those who don't have exclusionary conditions (screened beforehand). Follow-up points are same across site (4 mo, 7 mo followups), with the cognitive substudy adding in a 12 mo followup which is optional for UCD/UW but routine for UAB.		

Screening/Baseline Assessments. After obtaining informed consent, the first of three baseline visits will include medical history, physical exam, and *graded exercise test (GXT) with peak aerobic power (VO_{2peak})*. GXT (baseline): We will screen out volunteers with evidence of ischemic heart disease, serious arrhythmias, or abnormal heart rate/blood pressure responses to exercise. The test will begin at a comfortable walking speed and 0% elevation; speed will be maintained and the grade increased by 2% every 2 min, until the participant reaches volitional exhaustion or the test is otherwise terminated. Electrocardiogram will be monitored throughout. Procedures for minimizing risks during exercise testing are described below. VO_{2peak} will be used to prepare the prescriptions for aerobic exercise and to determine the effects of training (Δ baseline to week 16). The O_2 and CO_2 content of expired air will be measured continuously by open circuit spirometry and averaged every 30 sec using an automated online system. In the absence of evidence that VO_{2max} has been attained (≥ 2 of: a plateau in VO_2, respiratory exchange ratio ≥1.10, maximal heart rate within 10 beats of age-predicted), the maximum measured VO_2 will be deemed VO_{2peak}. Increases in VO_{2peak} in response to training will verify that the exercise was of sufficient intensity.

Baseline visit #2 will include a fasting blood draw (i.e., complete blood count, metabolic panel, HIV-1 RNA, CD4 count, PBMCs, FSH, and stored sample for future analyses) and *vastus lateralis* muscle biopsy **(this will be optional),** both collected between 8-10am. CD4 count does not to be measured if results from clinical care are available within the prior 12 months HIV-1 RNA if available within the prior 3 months and no reason to expect failure of treatment (I.e, stopped ART).. Complete blood count, complete metabolic panel, and thyroid stimulating hormone does not to be measured if results from clinical care is also available within the prior 3 months. The blood draw and the muscle biopsy will be repeated following the 16-week intervention. Blood labs may need to be repeated or redrawn at subsequent screening visits. Specimens of the *vastus lateralis* muscle will be obtained by percutaneous biopsy from fasted participants who have refrained from exercise for ≥ 48 hours. After cleansing the thigh with chlorhexidine, 1% lidocaine without epinephrine will be injected subcutaneously. A 3-5 mm incision will be made in the skin and fascia over the belly of the *vastus lateralis*, and 100-150 mg of muscle tissue will be removed using a Bergstrom side-cutting biopsy needle. The incision will be closed using Steri-strips; a compression wrap and ice will be applied for 30 minutes. Participants will be instructed on wound care and will be contacted by study staff 48-72 hours post-procedure to ensure healing. Dr. Erlandson has performed over 80 biopsies and PA Wright has performed over 50 biopsies with no prior complications and excellent tissue yield[125] (. Following the biopsy, study staff will explain the *Lee Fatigue Scale* (LFS) and use of the accelerometer (see below) to the participant.

Baseline visit #3. *Physical function and (optional) muscle ultrasound.* The **primary physical function outcome will be 400-MWT,** a well-established measure shown to better discriminate early physical function decline among higher functioning adults[126-128], and is a reliable outcome in clinical trials, including the LIFE Trial[129]. The Short Performance Physical Battery (SPPB) and a modified version (mSPPB)[130] will be obtained. The SPPB is an objective assessment of physical function associated with short-term mortality, disability, and hospitalizations[131,132]. The mSPPB improves discrimination of physical function by increasing repeat chair stands from 5 to 10, standing balance test for 30 seconds instead of 10, and adding a single leg stand. Physical function will be measured every 4 weeks by a research assistant blinded to intervention arm. The 400-MWT, SPPB, and mSPPB will be administered at both sites using standard scripts. Additional measures of frailty will include self-reported fatigue, weight loss, and exhaustion, and objective measures of grip strength by hand held dynamometer. The 400-MWT and the 10x chair stands from the mSPPB will be done every 4 weeks; the full physical function battery will be completed at baseline, week 16, and week 28. For the optional muscle ultrasound, we will collect sonographic images to provide estimates on lean muscle mass (aggregate muscle thickness, cm) and myosteatosis (grayscale values) using the Phillips Lumify L 12-4 linear array transducer. Sonographic estimates of lean muscle mass will be taken at the midpoint of the upper trapezius, pectoralis major, lateral deltoid, brachioradialis, rectus femoris, and tibialis anterior while the participant lays supine for 15-20 minutes.

Baseline visit #4: MRI/MRS. Prior to the initiation of exercise training, participants will undergo baseline MRI/MRS studies as detailed below. All of the proposed imaging modalities in the ancillary HEALTH+ Study Aims 1-3 can be completed within one-hour in the research scanner, located in the building adjacent to the Exercise Research Laboratory at UCD-AMC and the 14T MR Lab and Marcinek laboratory facilities at UW. Participants will be instructed to avoid vigorous activity for 2 days prior to the imaging studies. The imaging will be repeated during weeks 16, or within 4 weeks of the final exercise visit for PWH in the HEALTH study.

Patient-reported fatigue. Diurnal changes in fatigue will be assessed using the *LFS*[133]. This validated, 7-item visual analog scale asks participants to rate, on a scale of 0 to 10, how much fatigue they are feeling "right now". The *LFS* has been used to characterize fatigue profiles in PWH[134], allowing us to contextualize the effects seen with our exercise regimens within the larger population of PWH, and will help us to identify the fatigue phenotype most likely to benefit from HIIT or CME. Participants will be instructed to complete the *LFS* within 30 minutes of waking on 7 consecutive mornings and within 30 minutes before going to bed on the same 7 consecutive evenings. We have previously used longitudinal, daily assessments (including the *LFS*) to assess sleep quality[135] and PA[136], and have honed a procedure whereby we obtain >95% data. We will use the recommended *LFS* scoring in which all items are averaged into morning and evening fatigue scores. The 7-day averages will be our **primary fatigue outcomes: total morning fatigue and total evening fatigue scores**. We will also administer the PROMIS fatigue measure (an NIH common data element)[137], a global measure of fatigue that will provide additional valuable data (e.g., sleep quality), allowing us to understand the clinical effects of our interventions on fatigue. Fatigue assessments will be completed every 4 weeks throughout the exercise and behavioral intervention by a research assistant blinded to the intervention arm.

PA will be measured using the ActiGraph accelerometer (ActiGraph, LLC, Fort Walton Beach, FL)[125-127]. Participants will wear the monitor for 7-10 consecutive days on their nondominant hip. A valid wear cycle will have data recorded for ≥ 10 hours/day for ≥ 4 days[128-130]. Non-wear time will be defined as 0 counts/minute for ≥60 minutes. We will require consecutive epochs outside of the activity threshold for wear-time to resume. Participants not meeting standards will be asked to re-wear the ActiGraph. Data will be sampled at 30 Hz, using 60-second epochs, and the normal filter[131.] We have found that when given the second opportunity, 95% of participants met standards[132]. Activity ≥ 2690 counts/minute and ≥10 minutes will be defined as exercise[133].

Strength by 1-Repetition Maximum (1-RM) will be used to prepare exercise prescriptions and determine the effects of training. The 1-RM (maximal weight that can be lifted 1 time using correct form through the full range of motion) for upper and lower body RE will be performed at week 2, week 4, , and every 4 weeks through week 16. For participants who surpass the maximal load on a machine, an estimated 1RM will be conducted by having the participant perform as many reps as they can with the maximal load until exhaustion. The Bryzcki formula will then be used to determine the participant's estimated 1RM for that given time point.

DXA is the preferred method of assessing body composition[138]. Total body DXA scans will be performed at weeks 0 and 16 on Hologic instruments for measurement of total body mass, lean body mass, and fat mass. The operation of the DXA includes daily measurements of the spine phantom, weekly air scans, and tissue bar scans at least once per month. The reproducibility of DXA measurements was assessed in 40 women and men, aged 23-86 years, measured on 2 occasions over 1 month. The coefficients of variation (CV; mean, 95% confidence interval) for total body lean and fat mass were 0.7 (0.53, 0.83)% and 1.7 (1.32, 2.07)%[139].

Randomization. At the conclusion of Screening Visit 3, participants will be randomized to either HIIT or CME. Randomization sequences will be created by the study statistician (MaWhinney) and will be blocked by age, sex, and site to ensure a similar distribution between exercise arms. Due to observable differences in HIIT and CME, participants and trainers cannot be blinded to the treatment arms.

Intervention: Participants will complete 16 weeks of supervised CME or HIIT 3 days/week in the University of Colorado-Denver Exercise Research Laboratory, at the Prevention Center at Fred Hutch (University of Washington (UW) site, and at the Center of Exercise Medicine at University of Alabama. Participants will be given the option to complete 16 weeks of exercise at a recreational center if travel to the University of Colorado-Denver, University of Washinton, and University of Alabama at Birmingham is difficult. The recreation center must meet certain requirements (see risk section). Our study staff will visit the site in advance to ensure appropriate equipment is available. Any fees for membership will be covered by the study team (paid directly to the recreation center, not to the participant). Weeks 1-2 will focus on familiarization with the exercises at low intensity. These sessions will still occur at the University of Colorado-Denver center even if a participant choses to exercise at a local recreation center for the remainder of the 16 weeks. The intensity and duration of exercise will be progressed over the first 3-8 weeks to reach the individualized goals. The HIIT and CME interventions will be matched for exercise volume using standard equations for estimating caloric expenditure assuming 5 kcal/L O_2 [66]and 50 min/session duration for CME to meet the PA guidelines (Table 4). The total exercise time will differ by 8 minutes, but HIIT includes rest intervals and variety, which prior studies have shown is associated with greater enjoyment and physiologic benefits than CME.

HIIT. Following a 5-minute warm-up at 50% HRR (Heart rate reserve), high and moderate-intensity exercise bouts will alternate: Five bouts of 4-minute high-intensity exercise (90% HRR) will alternate with four 3-minute bouts of moderate-intensity exercise (50% HRR). The total exercise time will be 42 minutes.

CME. Following a 4 minute warm-up at 50% VO_{2peak}, the participant will walk for 50 continuous minutes at 60% HRR[140].

Resistance Exercise (For Both HIIT and CME). The initial goal will be to complete 3 sets of 8-10 repetitions of 3 exercises at low intensity (50% 1-RM) and then progress to moderate intensity (70-80% 1-RM)[140]. Exercise intensity will increase every 4 weeks or when participants can complete more than 8 repetitions with proper form at the prescribed weight. The exercises will be leg press, lateral pulldown, and a chest press, all on weight-stack equipment. Participants (CU only) who chose to exercise at a recreation facility will still return for in-person visits every 4 weeks and assessment of appropriate exercise intensity.

Supervised exercise sessions. Experienced research assistants (RA) will supervise exercise, interact frequently with participants, and encourage feedback regarding any discomfort. Participants will be instructed on maintaining a log of exercise that will be collected weekly and reviewed by Drs. Erlandson, Webel, Wheeler, and Jankowski. RA observations in conjunction with the exercise session logs will be used to modify the exercise prescriptions. The individualized exercise prescriptions will be geared toward increasing the exercise stimulus while avoiding unfavorable events. Barriers to completing exercise will be discussed and solutions offered. Blood pressure and resting heart rate will be measured before and after the first 6 sessions. In addition, blood pressure and resting heart rate will be measured before and after exercise sessions in these situations: 1) all HIIT sessions; 2) the first session after a medical hold or absence due to medical issue; 3) new signs or symptoms suggestive of metabolic, cardiovascular, or renal disease, regardless of the exercise status. As above, for those who decide to conduct their training at a recreational center (CU only), participants will attend 6 sessions with an RA prior to their training to learn proper exercise form, exercise documentation, and exercise understanding. For participants exercising at an outside facility, measured blood pressure will be reported to the study team with weekly exercise logs, sooner if blood pressure criteria met per the blood pressure monitoring handout.

Table 4. Example Aerobic Exercise Prescriptions

Participant weight = 78 kg and VO_{2peak} = 25.2 ml/kg/min				
	% HRR	*# Intervals*	*kcal*	*Total time*
CME	60	1 x 50 min	290	50 min
HIIT[a] (low)	50	4 x 3 min	288	42 min
HIIT (high)	90	5 x 4 min		
[a] alternating low/high-intensity, starting with low-intensity				

Variety booster exercise. Feedback during our prior intervention[23,106] indicated that participants want to learn about other exercise types. Thus, in addition to the 3 sessions/week, we will also host 2 monthly optional sessions incorporating a variety of other types of exercise (e.g., tai chi, yoga, elliptical, stationary bike).

Motivational interviewing (MI) To increase adherence to both conditions and promote a rigorous comparison of their physiological effects, exercise trainers will be taught to use MI, an evidence-based, communication strategy that identifies and enhances patients' own motivations for health behavior change[141].

Intervention fidelity. Exercise trainers will receive ~24 hours of training on HIIT & CME, exercise prescription, and MI. All trainers will be certified by the American College of Sports Medicine or hold academic degrees in exercise science and thus will be knowledgeable about the exercise components; standardized training will focus on our specific interventions, the needs of older PWH, and basic MI (e.g., reflective listening, staying motivated over time)[142,143]. The use of three basic resistance exercises and one mode of aerobic exercise (i.e., treadmill) reduces the variability in exercise training between sites. Standard exercise session logs will be used to collect data at each session. Fidelity will be established using observation of trainers during a simulated patient interaction at the first in-person team meeting at UCD-AMC, with the goal of ≥80% consistency[142]. We will video record ~ 10% of sessions with participants' consent, which will be coded by an independent rater to assess fidelity[144]. Exercise trainers at both sites will participate in ongoing supervision via monthly group video-conferences with Dr. Jankowski and the MI trainer, who will be supervised by Dr. Cook.

AIM 2. Evaluate bioenergetic mechanisms underlying HIIT and CME.

We ***hypothesize*** that PWH randomized to HIIT will have improved skeletal muscle and systemic (PBMC) mitochondrial bioenergetics (i.e., mitochondrial respiration rate and ETC activity). *The primary outcome is the change in state 3 respiration among PWH randomized to HIIT vs CME. Vastus lateralis* tissue specimens and a blood draw for PBMCs will be obtained at baseline and week 16 (Table 3). Skeletal muscle specimens will be trimmed of visible fat and connective tissue at the bedside, weighed, and then divided into 2 samples. Mitochondrial respiration will be conducted locally using fresh specimens; activity and content studies of frozen specimens will be completed at UCD-AMC. Both laboratories have extensively investigated mitochondria using multiple techniques including respiration, cellular signaling, and microscopy.

Mitochondrial Respiration. Sample 1 (skeletal muscle and isolated PBMCs) will be immediately transferred to laboratories of highly experienced mitochondrial researchers, Dr. Reusch[145-154] and Dr. Marcineck's. Laboratory personnel will be blinded to participant characteristics and other study data. Mitochondrial respiration will be measured using Oroboros Oxygraph-2K (O2k, OROBOROS INSTRUMENTS Corp., Innsbruck, Austria). Immediately after biopsy, skeletal muscle tissue is placed in ice-cold mitochondrial preservation buffer (BIOPS [10 mmol/L Ca-EGTA, 0.1 mmol/L free calcium, 20 mmol/L imidazole, 20 mmol/L taurine, 50 mmol/L K-MES, 0.5 mmol/L dithiothreitol, 6.56 mmol/L MgCl2, 5.77mmol/L ATP, 15mmol/L PCr, pH 7.1]). Muscle fibers are separated mechanically (in BIOPS and on ice), partially teased apart by fine forceps, permeabilized by incubation with saponin (30 ug/mL) in BIOPS on ice for 30 minutes, and then washed in mitochondrial respiration buffer (MiR06 [0.5 mmol/L EGTA, 3 mmol/L magnesium chloride, 60 mmol/L K-lactobionate, 20 mmol/L taurine, 10 mmol/L potassium phosphate, 20 mmol/L HEPES, 110 mmol/L sucrose, 1 g/L BSA, 280 units/mL catalase, pH 7.1]). A bundle of fibers (2–3 mg blotted wet weight) are added to prewarmed (37°C) MiR06 + 25 mmol/L blebbistatin in the O2k. Oxygen in the MiR06 is started at 400 mmol/L and maintained at >250 mmol/L. PBMCs will be washed, pelleted and resuspended in MiR06 before being added to O2k (attempting to place 1-3 $x10^6$ cells/chamber). PBMCs will be permeabilized in the O2k chamber with the addition of 35 µg/mL digitonin for 20 minutes. Oxygen in the MiR06 is started at ambient pressures and maintained >50 mmol/L. After respiration rates stabilized, substrates and inhibitors will be added to assess respiration rates. Rates will be measured following the addition of 5 mM pyruvate, 2 mM malate, and 10 mM glutamate (state 2 PMG), PMG with 2 mM adenosine diphosphate (ADP) (state 3 PMG), PMG, ADP, and 6 mM succinate (state 3 PMGS), and 2 µg/mL oligomycin (state 4 PMGS), and 0.5 µM of carbonyl cyanide 4-(trifluoromethoxy) phenylhydrazone (FCCP) will be added incrementally until maximal uncoupling (uncoupled state). Cytochrome c (10 µM) will be used to determine mitochondrial membrane damage. No significant differences in oxygen consumption following the addition of cytochrome c will indicate intact mitochondrial membranes. Oxygen, and all substrates, will be calibrated at saturating concentrations in the chambers with no possibility of rate limitations. These respiration techniques have been optimized for permeabilized skeletal muscle tissue and PBMCs [92,145-158]. After completing the experiment, fibers will be removed and PBMCs counted from the O2k chambers, and respiration rates normalized to weight or cell count. An area of consistent respiration rate of 3 minutes or longer will be representative of the various states. Respiration control ratios will be calculated as a ratio of state 3 PMGS/state 4 PMGS.

Mitochondrial Activity/Content. Sample 2 will be immediately placed in RNAse free vials, immersed in liquid nitrogen at the bedside, and then stored at -80° C for batch analysis. Samples from Dr. Webel will be shipped to Dr. Reusch's laboratory for analysis after all biopsies have been completed (Year 5). Frozen tissue will be homogenized using a MagNA Lyser (Roche Molecular Systems, Branchburg, NJ). Total RNA will be extracted from the supernatant using the Trizol Plus RNA Purification Kit (Life Technologies, Carlsbad, CA). Expression of citrate synthase and other mitochondrial markers of signaling, function and dynamics (AMPK, eNOS, PGC-1alpha, mitochondrial complexes I-V, Mnf1, OPA1) will be measured by established Western Blot techniques[159] using commercially available antibodies (Cell Signaling Technology, Inc., Beverly, MA). **Citrate synthase** (CS) activity will be assayed by adding 10 µM oxaloacetic acid (OAA) to 6-25 µg of tissue lysate protein (1-2 µg isolated mt protein) in 50 mMTris (pH 8.0), 100 µM DTNB and 100 µM acetyl CoA and measuring the increase in spectrophotometric absorbance at 412 nm for 3 min. CS specific activity will be measured by subtracting results obtained prior to the addition of OAA[145]. For **Complex (C) I+III** activity, 200 µM NADH will be added to 5-20 µg of tissue lysate protein (0.5-1 µg isolated mt protein) in 50 mM potassium phosphate (pH 7.5), 300 µM KCN, 50 µM cytochrome c and 1 mg/ml BSA and measuring the increase in absorbance at 550 nm for 3 min. CI+III specific activity will be measured by subtracting results obtained after 10 µM of rotenone was added. For **CII+III activity**, 50 µM cytochrome will be added to 20-70 µg of tissue lysate protein (1+ µg isolated mt protein) in 20 mM potassium phosphate (pH 7.5), 300 µM KCN and 10 mM succinate and measuring the increase in absorbance at 550 nm for 3 min. CII+III activity will be measured by subtracting results obtained prior to the addition of cytochrome c and confirming inhibition by the addition of 5 mM malonate. **CIV activity** will be assayed after oxidation of 15 µM reduced cytochrome c with 2-10 µg of tissue lysate protein in 50 mM potassium phosphate (pH 7.0) and following the decrease in absorbance at 550 nm for 3 min. Complex IV activity will be measured after accounting for the amount of inhibition after the addition of 300 µM KCN.

AIM 3. **Describe and compare the effect of a biobehavioral coaching intervention to enhance self-directed exercise.**

After completing 16 weeks of supervised exercise, participants will be randomized to control versus a 12-week coaching intervention using tailored text messages to support exercise adherence. We will conduct a mixed methods study assessing PA amount and mode and use interviews to elicit qualitative data on how to best sustain PA in this population. Our rationale for this aim is that despite almost a decade of research in this topic, *we lack effective strategies to maintain PA in PWH*, indicating a need for foundational data on how to best support PWH in sustaining PA habits. A longitudinal, mixed methods approach coupled with a coaching intervention is ideally suited to generate these data. The proposed

study provides an opportunity to efficiently test an innovative strategy of coaching and exercise type (HIIT vs CME), to fill important gaps in the literature.

Participants. HEALTH participants (up to *n*=180) will complete quantitative assessments (i.e. accelerometry) during their outcome assessments at baseline, week 16 (after the 16-week exercise intervention), week 4, 8, 12 of biobehavioral coaching and week 28 (after the 12-week coaching intervention). During the consent process, 20 participants at each site (*n*=40, including at least 15 in HIIT or CME arms and 15 women) will have the opportunity to co-enroll in a qualitative substudy. These participants will complete three one-on-one interviews (at weeks 0, 16, 28) to capture perspectives on HIIT and CME, and how to sustain PA.

Procedures/Outcome Measures*:*

Randomization. After the conclusion of the exercise intervention, participants will be randomized 1:1 (with even allocation of HIIT vs CME) to receive the coaching or control intervention (details below).

Quantitative Measures. **PA** will be measured with a widely-used and validated measure, the ActiGraph accelerometer (ActiGraph, LLC, Fort Walton Beach, FL), as described in Aim 1[125-127].**Primary exercise endpoints** are (1) time spent in moderate-to-vigorous PA (MVPA), and (2) steps per day. These endpoints will be set with the adult cut-points for tri-axial accelerometers[134]. All participants will complete a daily log during the maintenance phase to track aerobic and resistance exercise. This log will include the time, type, duration, and setting of exercise completed each day. It will be triangulated with the accelerometry data and reported descriptively.

Figure 4: Exemplar questions to understand perceptions of HIIT, CME and Sustaining Long-Term Exercise in PWH

Context

- Tell me about your prior experiences with exercise? Probes: What did you do? Why (e.g., doctor prescribed, athletics, friends did it)? When was this? What stops you from or helps you to exercise regularly?

Self-Efficacy

- Do you think you can engage in a regular, intense exercise program? Why or why not? How do your prior experiences influence this?
- How has the HIIT or CME (tailored to the group) training impacting your belief that you can engage in long-term, regular, exercise program?

Outcome Expectations and Goals

- If you engage in regular, intense exercise over the long term what do you think will happen to you? Prompts: your health, your body, your relationships [baseline]? How has your participation in the HIIT or CME programs changed how you think about how exercise impacts you?
- What are your goals for exercise habits? [prompts: frequency, intensity]. How has this changed? What effect did the texting have?

Qualitative Measures. **One-on-one Interviews (this will be optional).** First, we will pilot test an interview guide on 2-3 PWH at UWand UCD-AMC and revise it accordingly. A final guide will be used to direct subsequent interviews consistently at both sites. The interviews will take place in a secure, private location. Questions will address the participants' perceptions of exercise; experiences with HIIT, CME, or resistance training; the coaching intervention; and what they think will help them sustain PA over the long-term (Fig. 4). If a participant withdraws from the study, he/she may be offered a withdrawal interview to explore reasons for withdrawal and/or ways to improve the study intervention. Interviews will take ~ 30 minutes, be audio-recorded, and transcribed verbatim. Dr. Webel has over 15 years of experience designing, implementing, and analyzing data from qualitative studies and has successfully trained and managed qualitative data collectors across sites, obtaining high-quality data[160,161].

Intervention. *Coaching:* The coaching intervention will consist of daily text messages tailored to the individual participant's self-reported symptom experiences and barriers to exercise on that specific day. To enhance motivation, tailored messages will be generated automatically by an algorithm[162] but will be "signed" by the participant's exercise trainer to enhance the interpersonal connection. Tailored messages will address a range of possible barriers to adherence based on past research, and will provide advice and guidance (Table 5). Additional message refinements will be developed based on participants' feedback about PA barriers and facilitators during qualitative interviews. Finally, text messages will be varied each week so that even if participants continue to report the same barriers they receive different text messages; this strategy was identified in prior research as key to prevent boredom and maintain participants' attention[162].

Control: The control group will receive general weekly texts from the study team (i.e., "Hope you are doing well!"), and reminding them of their next study appointments. These text messages are primarily social/generic in content and serve to maintain involvement and enhance retention of the control group.

Monthly Check-in. All participants will complete in-person physical function and fatigue assessments every 4 weeks (including CU participants who chose to exercise at a recreation center). During these visits, for the coaching group only, the trainer will ask about current PA, barriers to adherence, and any factors that help to maintain PA over time. Trainers will offer support using the MI approach.

Post Intervention Survey: Participants who have completed the entirety of the intervention at UCD and UW will be given the opportunity to answer prior exercise related questions to better explore how previous experience with exercise might

influence people's ability and wilingness to keep exercising after the intervetion. These surveys will be sent via email using a one time RedCap survey link.

COGNITIVE SUBSTUDY

Newly enrolled participants at UW/UCD sites will have the option to enroll in the cognitive substudy, which per the Timeline table above, will include cognitive assessments at current study visits (baseline, 16 weeks and 28 weeks) and a new 48 week visit which will include cognitive assessment, blood draw, and psychological mechanisms of adherence measures (which includes text messaging surveys and traditional paper pencil questionnaires). Further detail below. All enrolled UAB site participants will receive these assesments.

Cognitive Function will be assessed using a gold-standard battery from the National Alzheimer's Coordinating Center (NACC) Universal Data Set (UDS), which balances participant burden with acquiring a comprehensive assessment. The assessment will be conducted by staff who are blind to intervention group. Staff will be trained and certified by the study PI and will be supervised weekly via meetings and communication. 30% of batteries will undergo double scoring by another staff member and 10% of batteries will be triple scored by the study PI. The PI will also observe assessments quarterly (either in person or video).

We will examine several outcomes, including continuous composites (corrected and uncorrected for demographics) across each domain, as well as a global cognitive functioning composite. We will also examine self-reported cognitive symptoms and declines in daily function. Finally, we will use cognitive T scores and subjective symptoms and everyday functioning declines to generate cognitive diagnoses. Though there are many approaches to operationalizing cognitive impairment in HIV, and in MCI, exist, we will employ validated approaches that are consistently used in neuroAIDS. Despite subtle differences in definitions, most include mild impairment in cognitive function (e.g., ~1 SD below mean on 2 tests/domains), and evidence of either subjective cognitive deficits or declines in daily function.

One-hour Neurocognitive Assessment Battery	
Domain	**Measure**
Depression and Everyday Functioning	**Depression:** Patient Health Questionnaire 9-item Depression; **Everyday Function & Cognitive Symptoms:** Functional Activities Questionnaire, Cognitive Failures Questionnaire;
Neurocognitive Assessment	**Cognitive Status:** Test of Premorbid Functioning, TICS; **Verbal IQ:** WRAT 3 Word Reading; **Attention/Working Memory:** WAIS-IV Digit Span Forward and Backward; **Processing Speed:** Trails A, SDMT, Stroop Color-Word Reading; **Executive Function:** Trails B, Stroop Interference; **Verbal Fluency:** Animals, FAS; **Visuospatial:** Benson Complex Figure Copy; **Learning and Memory:** Craft Story Memory, Benson Complex Figure

Blood Biomarkers. This study will leverage blood being collected in the primary study, and collect additional blood at the new 12 month visit. Identical procedures for blood draws will be done at UAB site. The blood draw procedure for the primary study is described in Baseline Visit #2 above. De-identified frozen samples will be shipped to University of Alabama at Birmingham for assay in the UAB Metabolism Core Laboratory housed under the UAB Nutrition Obesity Research Center. The following markers will be measured in duplicate with chemiluminescence immunoassay or enzyme-linked immunosorbent assay (ELISA) with the following assays: BDNF (R&D Systems [Minneapolis, MN] Human Free BDNF Quantikine ELISA kits), VEGF (MesoScale Discovery [Rockville, MD] Human Cytokine Panel I kits), IGF-1 (ALPCO [Salem, NH] IGF-1 ELISA kits), IL-6 and TNF-a (MesoScale Discovery [Rockville, MD] Human V-Plex Proinflammatory Panel I kits). hsCRP will be measured on a Stanbio Sirus (Boerne, TX) analyzer using Pointe Scientific (Canton, MI) turbidometric reagent.

Neuroimaging. MRI data will be acquired from participants **at UAB only** (n=50) at baseline and 4 months. Participants will undergo ~1 hour of scanning at each time point, using a 3T Siemens Prisma scanner with a 64 channel coil, housed at the UAB Civitan International Neuroimaging Laboratory (CINL), where Co-I Visscher is the Co-Director. Participants will be screened for any contraindications for MRI (described below in risks). We will acquire anatomical (T1 and T2 scans), arterial spin labeling (pseudo-continuous ASL), and resting state blood oxygenation level dependent (BOLD) scans. ASL, a non-invasive approach to measuring cerebral blood flow (CBF), is a MRI technique that measures tissue perfusion (blood flow), by using magnetically-labeled arterial blood water protons as an endogenous tracer. ASL has demonstrated high consistency with positron emission tomography PET measurement of CBF, and is emerging in popularity due to its advantages in terms of cost-effectiveness and safety. General quality assurance procedures will be followed as data are acquired, including quality control checks after each session. Mean global CBF, and regional blood flow to the hippocampus will be measured for each participant based on ASL scans. We will also measure changes in total gray matter volume and hippocampal volume (mm3) using Freesurfer. Strength of connectivity within the default mode network will also be

examined based on resting state BOLD data (i.e., average correlations of BOLD-signal time series of distributed brain regions as in previous work). BOLD data will be preprocessed according to strict quality control methods, including motion scrubbing, implemented by XCP engine with fMRI prep, and regression of confounds including but not limited to motion, heartbeat and respiration.

Psychological mechanisms of adherence (MoA) measures will be assessed at the new 12-month visit only. The trait-level measures (i.e., paper/pencil surveys completed in person) capture aggregate perceptions about one's self, whereas text message (i.e. ecological momentary assessment [EMA]) (state-level) items reflect experiences in the moment. The measures chosen are theory-driven, align with the NIH Science of Behavior Change. As noted in the Table below, abbreviated versions of select measures used in lab visits will be used in EMA to reduce participant burden and increase compliance.

Following the 12 month visit, the EMA will include 7-days of twice daily texts (quasi-random times at morning and evening) using their own mobile device. **Participants will already be familiar with texting procedures following the behavioral coaching intervention (part of primary study, described above and below).** The Twilio 3rd party add on feature in RedCap will be used to generate links to our RedCap survey (assessing items indicated in the Table) housed within the Denver RedCap server and text message them to participant's cell phones. No data is sent to Twilio and no PHI is collected. Twilio is HIPPA compliant and is vetted by RedCAP admin/Denver CCTSI. We piloted the survey, which takes <five minutes. If a participant does not respond to a survey, a reminder message will be sent one hour later. If a participant has not responded to any survey for 24 hours, we will contact them to troubleshoot and encourage reporting. **Actigraphy will also be worn for 7 days, using procedures described above for the Primary Study.**

We will administer individual interviews with a subset of participants (~n=25) to determine factors that drive or impede long-term PA after having been in a supervised intervention.

Mechanisms of Adherence Measures in the New 12 month Follow Up	
Construct	**Measure**
Self-Efficacy	**Lab and EMA:** 9-item self-efficacy exercise (SEE) scale[145] assesses expectations related to ability to continue to exercise in the face of barriers (How confident are you right now that you could exercise three times per week for 20 minutes if: [e.g., "You did not enjoy it", "You were too busy", "You had to exercise alone"]). **EMA in am and pm; items use words "today" and "tomorrow".**
Motivations	**Lab:** 19-item Behavioral Regulation in Exercise Questionnaire (BREQ-3)[146] assesses Amotivation (four items), External Regulation (four items), Introjected Regulation (three items), Identified Regulation (four items), and Intrinsic Regulation (four items). Participants asked "Why do you engage in exercise?" and rate how true each statement is for them using Likert scale (e.g., "*I exercise because it's fun"*). **Lab and EMA:** 37-item Exercise Motivations Inventory (EMI-2)[147] assesses intrinsic and extrinsic motives to exercise. Participants indicate how true each statement is for them using Likert scale, with the following subscales: Health & Fitness, Social/Emotional, Weight Management, Stress Management, Enjoyment, Appearance**. EMA in am; items use word "today"; items only include general item for each 6 subscale domains (e.g., "If I exercise today, it will be for… Health and Fitness").**
Self-Regulation Strategies	**Lab and EMA:** 12-item Physical Activity Self-Regulation scale (PASR-12)[148] measures use of six strategies including self-monitoring, goal setting, eliciting social support, reinforcement, time management, and relapse prevention. Participants asked to rate how often they used each self-regulation strategy in the past 4 weeks on a Likert scale. **EMA in pm; items use word "today" (e.g., "When I exercised today, I rearranged my schedule to ensure I had time for PA"). If no PA is reported, measure is skipped.**
Outcome Expectations	**Lab and EMA:** 16-item Decisional Balance (DB) Scale for Exercise[112, 149] assess positive and negative outcome expectations and includes 10 pros (e.g., "I would feel less stressed if I exercised regularly") and 6 cons ("Regular exercise would take too much of my time"); DB score is pros minus cons. **EMA in am; items use word "today".**
Affective States	**EMA:** 12-item Exercise-induced Feeling Inventory (EFI)[112, 150] captures four feeling states: revitalization (e.g., energetic, refreshed), tranquility (e.g., calm, relaxed), positive engagement (e.g., enthusiastic, happy), and physical exhaustion (e.g., fatigued, tired). Four additional items[110] included to assess negative affect (e.g., anxious, stress, sad). **EMA in am, pm, and PA event contingent.**
Social Cohesion/Support	**Lab:** Social Cohesion Measure[101]: Participant selects agreement based on Likert scale to the following 4 statements: 1) People in this neighborhood help each other out (help availability), 2) There are people I can count on in this neighborhood (accountability in neighbors), 3) People in this neighborhood can be trusted (trust in neighbors), and 4) This is a close-knit neighborhood (close-knit neighbors). **EMA:** Recent Social Interaction: "Did you have a stressful/problematic or positive/uplifting social interaction in the past few hours". YES/NO for positive/negative interaction. **EMA in am, pm**

D. Description, Risks and Justification of Procedures and Data Collection Tools:

Muscle biopsy. Participants agreeing to muscle biopsy will have a biopsy prior to and at the completion of the 16 week intervention. Participants will be advised to refrain from any physical activity for at least 48 hours following the biopsy. Non-steroidal anti-inflammatories or aspirin are held for 7 days prior to the biopsy. If participants are taking direct oral

anticoagulants, this will be held for 48 hours prior to the procedure (72 hours if creatinine clearance is 30-50 and taking dabigatran) if approved by their primary provider. Therapy can be resumed 24 hours after the procedure, or as instructed by their physician. At study completion, subjects will be asked to return within 10 days of the final exercise session for a muscle biopsy. The exercise intervention will begin >48 hours after the initial biopsy, but within 28 days. Participants will be asked to abstain from alcohol or caffeinated beverages after 1300h and to fast from any food or drink beginning at 9pm with the exception of water. The biopsy will be completed prior to 10am local time. Percutaneous samples of the vastus lateralis muscle will be obtained. After cleansing the area of the thigh with antiseptic (e.g., chlorhexidine, Betadine solution), 1% lidocaine (without epinephrine) will be injected under the skin. A 3-5 mm incision will be made in the skin and fascia over the belly of the vastus lateralis, and 100-150 mg of muscle tissue will be removed using a Bergstrom side-cutting biopsy needle with suction applied. The incision will be closed and a compression wrap and ice will be applied to the incision area for 30-45 minutes. The patient will be given instructions for wound care before discharge.

Risks: The risks associated with muscle biopsy include brief, mild burning pain from the local anesthetic (lidocaine), more than mild discomfort during the acquisition of tissue (about 10% of cases), and infection (less than 0.4% of cases). Allergy to the anesthetic (skin swelling or rash) occurs rarely. There may be persistent numbness in the biopsy area.

Plan to Minimize Risk: Risks of the muscle biopsy procedure will be minimized by having a trained clinician perform the procedure on participants who meet the biopsy-specific criteria listed above. Dr. Erlandson has previously performed more than 80 biopsies and PA Wright has completed more than 50 biopsies. Participants will be observed following the procedure for any adverse events and given strict instructions for wound care. A phone call will be made within 48-72 h of the biopsy procedure to assess wound healing with a study clinician. Additionally, the study will have a safety officer. Drs. Erlandson and Webel will review biopsy and exercise safety with the DSMBr every 6 months.

Justification: Skeletal muscle mitochondria are reflective of insults that may have occurred decades earlier, whereas mitochondrial studies obtained through peripheral blood would only reflect changes over a much shorter time period. Thus the muscle specimens provide a window into mechanisms well beyond what can be collected less invasively and reflect changes in the tissue targeted with the intervention.

Exercise testing and training: *A*ll participants will engage in a 16-week randomized, supervised exercise intervention (high-intensity interval training [HIIT] vs continuous moderate exercise [CME], followed by a 12-week exercise maintenance intervention in which participants are also randomized to a coaching vs control intervention. The exercise prescription will be based on baseline measure of VO2 maximum (or peak) and 1-RM measurements.

Maximal aerobic power (VO_2 max). The measurement of VO_2max (or peak) will be used to formulate the prescription for CEx at the screening visit. Increases in VO_2max in response to exercise training will also verify that the exercise was of sufficient intensity to induce cardiorespiratory adaptations. During an initial 5-min warm-up, walking speed will be adjusted to elicit a HR that is ~70% of maximal HR (from the screening GXT). Speed will then be held constant and the grade of the treadmill will be increased by 2% every 2 minutes until volitional exhaustion or until the test is stopped (see section 4.1.2b). The O_2 and CO_2 content of expired air will be measured continuously by open circuit spirometry and averaged every 30 sec using an automated online system (TrueMax 2400; ParvoMedics, Sandy, UT). Objective evidence that VO_2max has been attained will include at least 2 of the following: a plateau in VO_2 despite an increased energy demand, a respiratory exchange ratio in excess of 1.10, and a maximal HR within 10 beats of the age-predicted value. In the absence of these benchmarks, the maximum measured VO_2 will be deemed VO_2 peak.

Muscle strength (1-RM). Muscle strength will be evaluated as the 1-RM (the maximal weight that can be lifted only 1 time using correct lifting form through the full range of motion) for the upper and lower body REx performed during weeks 1-16. 1RMs will be measured at week 0 and every 4 weeks to week 20. The change in muscle strength from week 0 to 16 will be a secondary outcome measure.

Exercise Intervention. Participants will be assigned with equal probability to one of the two exercise intervention arms (high intensity interval training [HIIT] or continuous moderate intensity exercise [CME]) following completion of screening procedures. Randomization procedures will be site-specific, and use permuted blocks with stratification by sex and 10-year age categories (i.e., 50-59 years, 60-69 years, 70-80 years), to assure similar distribution in each arm. The allocation to study arm will remain blinded (masked) to the research assistant conducting the physical function assessments and to laboratory personnel.

All participants will begin with a 2-week supervised, low-intensity exercise acclimation with an experienced research assistant. The initial goal will be to walk on a treadmill for 20-30 continuous minutes at low-intensity (30-40% of maximal aerobic power [VO_2max]) and complete 3 sets of 8 repetitions at low-intensity (40-50% of the one-repetition maximum; 1-RM) 3 or 4 days/week. This will facilitate comfort with study equipment and minimize injury.

At 2 weeks, all participants will complete an additional 14 weeks of moderate- intensity continuous exercise or HIIT in the University of Colorado-Denver Exercise Research Laboratory, at the Prevention Center at Fred Hutch (UW), the Center for Exercise Medicine at University of Alabama, or at a recreational center of their choosing. Weeks 1-2 will focus on familiarization with the exercises at low intensity. The intensity and duration of exercise will be progressed over the first 3-8 weeks to reach the individualized goals. The HIIT and CME interventions will be matched for exercise volume using standard equations for estimating caloric expenditure assuming 5 kcal/L O_2 [66]and 50 min/session duration for CME to meet the PA guidelines (Table 4). The total exercise time will differ by 8 minutes, but HIIT includes rest intervals and variety, which prior studies have shown is associated with greater enjoyment and physiologic benefits than CME.

HIIT. Following a 5-minute warm-up at 50% HRR, high and moderate-intensity exercise bouts will alternate: Five bouts of 4-minute high-intensity exercise (90% HRR) will alternate with four 3-minute bouts of moderate-intensity exercise (50% HRR). The total exercise time will be 42 minutes.

CME. Following a 4 minute warm-up at 50%HRR, the participant will walk for 50 continuous minutes at 60% HRR[140].

Resistance Exercise (For Both HIIT and CME). The initial goal will be to complete 3 sets of 8-10 repetitions of 3 exercises at low intensity (50% 1-RM) and then progress to moderate intensity (70-80% 1-RM)[140]. Exercise intensity will increase every 4 weeks or when participants can complete more than 8 repetitions with proper form at the prescribed weight. The exercises will be leg press, lateral pulldown, and a chest press, all on weight-stack equipment.

Supervised exercise sessions. Experienced research assistants (RA) will supervise exercise, interact frequently with participants, and encourage feedback regarding any discomfort. Participants will be instructed on maintaining a log of exercise that will be collected weekly and reviewed by Drs. Erlandson, Webel, Wheeler, and Jankowski. RA observations in conjunction with the exercise session logs will be used to modify the exercise prescriptions. The individualized exercise prescriptions will be geared toward increasing the exercise stimulus while avoiding unfavorable events. Barriers to completing exercise will be discussed and solutions offered. Heart rate monitoring during each exercise session (continuously) will allow for immediate feedback on achieving target goals.

Table 4. Example Aerobic Exercise Prescriptions

Participant weight = 78 kg and VO_{2peak} = 25.2 ml/kg/min

	HRR	*# Intervals*	*kcal*	*Total time*
CME	60	1 x 50 min	290	50 min
HIIT[a] (low)	50	4 x 3 min	288	42 min
HIIT (high)	90	5 x 4 min		

[a] alternating low/high-intensity, starting with low-intensity

Variety booster exercise. Feedback during our prior intervention[23,106] indicated that participants want to learn about other exercise types. Thus, in addition to the 3 sessions/week, we will provide suggestions to try a variety of other types of exercise (e.g., tai chi, yoga, elliptical, stationary bike).

Risks: The potential risks of exercise testing and training include development of ventricular arrhythmia, myocardial infarction, cardiac arrest, and death, as well as the less serious problems of injury to tendons, ligaments, joints, and muscles. Measures taken to minimize these risks are detailed below.

- Endpoints for exercise tests: In asymptomatic individuals who do not develop cardiovascular abnormalities, the endpoint for the maximal exercise tests will be achieving 85% of age-predicted maximal heart rate, fatigue that forces cessation of exercise, or increasingly unstable gait. The criteria that will be used to stop the exercise test before meeting the above criteria include the development of: (a) ST-segment depression of more than 0.2 mV that is either horizontal, downsloping, or slowly upsloping (less than 1 mV/sec) and lasts for 0.08 sec, or ST-segment elevation greater than 0.1 mV; (b) chest pain or discomfort; (c) serious arrhythmias, including multifocal PVCs, ventricular tachycardia, or sustained atrial tachyarrhythmias; (d) development of A-V block or other conduction defects; (e) a fall of systolic blood pressure of 10 mmHg or greater from the peak level with increasing exercise intensity; (f) diastolic blood pressure above 110 mmHg or systolic above 220 mmHg; (g) dizziness; (h) ataxic gait; and (i) pallor or cyanosis. If a subject is noted to have osteoporosis (T-score <-2.5, upon screening, he or she will be referred to their primary care physician to discuss the potential risks and benefits of exercise and the need for immediate or delayed treatment for osteoporosis prior to initiating the study. The risks associated with the muscular strength tests are musculoskeletal pain, fatigue, dizziness, and syncope. These risks will be minimized by providing one-on-one instruction in proper exercise

technique on multiple days prior to testing. Workloads will be increased gradually to elicit moderate to maximal effort, and a brief rest period will follow each attempt. Appropriate warm-up and cool-down periods will be included in the strength test procedures. Blood pressure will be monitored before and after exercise for the first 6 sessions. The potential for a serious adverse event to occur with resistance exercise testing is minimal in persons who have undergone prior medical screening. In 20,000 maximal dynamic strength tests in women and men aged 18 to 93 years, no cardiovascular events were reported [3].

- Training of personnel: All personnel assisting with the administration of screening treadmill tests and with the exercise training will have Basic Life Support certification and at least 1 member of the testing team will have Advanced Cardiac Life Support certification. In accordance with current recommendations of the American Heart Association and American College of Sports Medicine, a clinician with exercise stress testing experience in older adults or an exercise specialist technician with experience testing older adults will directly supervise screening treadmill tests; a physician will be immediately available in the facility if not directly administering these screening tests. A physician will interpret ECG and blood pressure responses for all screening treadmill tests. For subsequent exercise testing (e.g., strength testing), the physician will provide written orders, based on the results of the screening test, regarding whether a clinician must be present for, or directly supervise, the follow-up tests. For participants who decide to complete the intervention at a recreational center, all staff and employees at the location will be verified to have Basic Life Support certification, an automated external defibrillator (AED) device on hand, and an employee available at all work hours by an RA prior to the start of the intervention.
- Screening of volunteers: To minimize the risks of exercise testing in older subjects, testing will be conducted only after the volunteer is examined by a clinician and after a resting ECG is obtained and evaluated. During exercise testing, the ECG is monitored continuously and BP is measured frequently. Exercise tests are terminated if any of the American College of Sports Medicine absolute (and, in some cases, relative) stopping criteria are met [4]. The American Heart Association-recommended emergency equipment and supplies will be available, including: automatic external defibrillator; portable oxygen tank, nasal cannula, ventimask, non-rebreathing mask, and appropriate tubing to connect to the oxygen tank; oral airways; bag-valve-mask hand respirator; syringes and needles; IV tubing, solutions, and stand; and adhesive tape. All exercise trainers will have current Basic Life Support certification. The Exercise Research Laboratory (ERL) at UCD-AMC, at the exercise facilities at the Prevention Center at Fred Hutchboth, and The Center of Exercise Medicine at University of Alabama operate as 911 emergency response facilities should any emergencies arise.

Justification: Exercise is routinely recommended in older adults for its known benefits on multiple systems. Furthermore, stress testing is a routine clinical screening test if recommending that older adults with risk of cardiovascular disease plan to begin an exercise intervention. Thus the procedures are consistent with routine clinical practice. If any injuries occur during the study, participation will be placed on hold until cleared by the participant's physician or other healthcare provider to return to full exercise. If the participant's exercise hold is longer than 2 weeks, the exercise may be gradually increased to return to the same intensity, with exercise ramp-up at the discretion of the study team and based on the reason for holding exercise.

DXA: Whole body densitometry (DXA) scan will be performed: Body composition comparisons will include total body fat free mass, body fat mass, trunk fat, trunk to limb fat ratio, and appendicular lean tissue mass. Determination of sarcopenic obesity will be calculated from appendicular skeletal lean tissue mass divided by squared height (kg/m^2), with $< 7.26\ kg/m^2$ in men or $< 5.45\ kg/m^2$ in women suggesting presence of sarcopenic obesity based on limited prior studies.

Risks: The DXA (for measures of body composition) involves exposure to ionizing radiation. The DXA scans (total body,) at 2 times during the study involve a total effective radiation exposure of about 60 mrems. DXA involves <3% of the annual maximum non-therapeutic radiation exposure to the whole body recommended by the FDA (5000 mrem/year). Urine pregnancy will not be performed prior to DXA scans, as all women will be post- childbearing state (ie, post-menopausal).

Plans to minimize risk: The risk of radiation exposure is minimized by having trained technicians administer the DXA, thereby reducing the likelihood of needing repeat assessments.

Justification: DXA is a routine test obtained in clinical practice and will provide important data regarding the impact of exercise on lean and fat mass.

Physical function tests and Physical Activity Assessments: The **primary physical function outcome will be 400-MWT,** a well-established measure shown to better discriminate early physical function decline among higher functioning adults[126-128], and is a reliable outcome in clinical trials, including the LIFE Trial[129]. The Short Performance Physical Battery (SPPB) and a modified version (mSPPB)[130] will be obtained. The SPPB is an objective assessment of physical function associated with short-term mortality, disability, and hospitalizations[131,132]. The mSPPB improves discrimination of physical function by increasing repeat chair stands from 5 to 10, standing balance test for 30 seconds instead of 10, and adding a single leg stand. Physical function will be measured every 4 weeks by a research assistant blinded to intervention arm. The 400-MWT, SPPB, and mSPPB will be administered at both sites using standard scripts. *PA* will be measured using the ActiGraph accelerometer (ActiGraph, LLC, Fort Walton Beach, FL)[125-127]. Participants will wear the monitor for 7-10 consecutive days on their nondominant hip. A valid wear cycle will have data recorded for ≥ 10 hours/day for ≥ 4 days[128-130]. Non-wear time will be defined as 0 counts/minute for ≥60 minutes. We will require consecutive epochs outside of the activity threshold for wear-time to resume. Participants not meeting standards will be asked to re-wear the ActiGraph. Data will be sampled at 30 Hz, using 60-second epochs, and the normal filter[131.] We have found that when given the second opportunity, 95% of participants met standards[132]. Activity ≥ 2690 counts/minute and ≥10 minutes will be defined as exercise[133].

Risk: The risks associated with the physical function tests are minimal and include a) slight muscular soreness or strain; b) a small possibility of loss of balance or fall, and c) a very small possibility of angina from overexertion.

Plans to minimize risk: Physical function assessments are meant to mimic a patient's daily activities, such as walking across the room, rising from a chair, and balancing to reach for an overhead object. These assessments pose little risk beyond what would be encountered in a day's activities. To minimize the risks of physical function testing, an experienced examiner will administer the tests and instruct participants to stop if they are uncomfortable or fearful at any time during the test. Participants will be allowed ample rest time between tests.

Justification: Physical function measures are predictive of subsequent disability, hospitalizations, falls, and mortality and are safely administered in multiple large cohorts of aging individuals.

Venipuncture:

Risk: There is a small risk of local hematoma or infection associated with blood sampling.

Plans to minimize risk: The risks of hematoma and infection are minimized by having trained clinical personnel perform the procedures using sterile techniques.

Justification: Laboratory measures will be assessed pre-exercise to ensure that participants are safe for the intervention and will be utilized for the mitochondrial assessments. If the peripheral blood mitochondrial assessments are similar to that of the muscle biopsy, this would provide justification for avoiding muscle biopsy in the future.

Fasting:

Risk**:** There is a risk of hunger, and a small risk of dizziness, lightheadness, low blood sugar, and fatigue during fasting.

Plans to minimize risk: The risks of fasting will be minimized by encouraging participants to stay hydrated with water prior to the visit. For diabetics, diabetes medications will be held until the participant can have a snack.

Justification: Laboratory measures need to be obtained in the fasting state to minimize confounding and ensure validity.

Stool collection (this will be optional): There is risk of embarrassment or exposure to feces with sample collection.

Plans to minimize risk. Participants will be provided with instructions and a kit to safely collect the sample. This will be optional part of the study.

Justification: Due to differences in microbiome with exercise seen in our preliminary work, we will collect stool samples for microbiome and short chain fatty acids at baseline and week 16.

Questionnaires:

1. *Lee Fatigue Scale*. This validated, 7-item visual analog scale asks participants to rate, on a scale of 0 to 10, how much fatigue they are feeling "right now". The *LFS* has been used to characterize fatigue profiles in PWH[134], allowing us to contextualize the effects seen with our exercise regimens within the larger population of PWH, and will help us to identify the fatigue phenotype most likely to benefit from HIIT or CME. Participants will be instructed to complete the *LFS* within 30 minutes of waking on 7 consecutive mornings and within 30 minutes before going to bed on the same 7 consecutive evenings. We have previously used longitudinal, daily assessments (including the *LFS*) to assess sleep quality[135] and PA[136], and have honed a procedure whereby we obtain >95% data. We will use the recommended *LFS* scoring in which all items are averaged into morning and evening fatigue scores. The 7-day averages will be our **primary fatigue outcomes: total morning fatigue and total evening fatigue scores**.
2. PROMIS fatigue measure (an NIH common data element)[137], a global measure of fatigue that will provide additional valuable data (e.g., sleep quality), allowing us to understand the clinical effects of our interventions on fatigue. Fatigue assessments will be completed every 4 weeks throughout the exercise and behavioral intervention by a research assistant blinded to the intervention arm.
3. *HIV Symptom Index*, a validated measure of 20 common HIV-related symptoms
4. *The Friendship Scale*, a validated 6-item measure of isolation.
5. Patient Health Questionnaire (PHQ)-9
6. Pittsburgh Sleep Quality Index
7. Epworth Sleepiness Scale
8. PROMIS Physical function
9. Brief Falls Assessment
10. Diet log: Self-reported food intake over 3 days will be collected between baseline visits #2 and 3 using the CTRC standardized collection form.
11. Microbiome Questionnaire
12. Demographics questionnaire
13. Monthly Health Status
14. LURN Symptom Index-10
15. Technology Acceptance Survey
16. Functional Activities questionnaire and Cognitive Failures questionnaire
17. Psychological mechanisms of adherence to exercise (measures described in Table above)
18. Ultrasound Feasibility & Acceptability Questionnaire
19. Connor Davidson Resilience Scale
20. Prior Intervention Exercise Questionnaire (UCD and UW Only)

Risks There is minimal risk associated with completing these questionnaires. If someone indicates extremely poor well-being on the well-being questionnaire, they may be referred to the emergency room or their provider, after discussion with the patient and assessment of any harm.

Plans to minimize risk Participants will be instructed to take breaks or skip questions on the surveys if they feel uncomfortable completing them.

Benefit: A better understanding of how exercise models impact symptoms and isolation in a population that disproportionately experiences high symptom burden will allow us to understanding if we can improve these symptoms using nonpharmacologial strategies. The ability to counsel patients about if, how much, and what type of exercise will reduce fatigue and other symptoms will improve the quality of life of people living with HIV.

Cognitive Assessment

Risk**:** Participants may express distress or mental fatigue during/after engaging in the cognitive assessment.

Plans to minimize risk: Any potential distress that could be reported during cognitive testing will be mitigated by employing skilled cognitive testers who are trained to assure participants that the tests are designed so that no one can do well on all of the tests, and there will be a point at which everyone can no longer do well. We have also selected a brief 1 hour battery to reduce participant burden and mental fatigue. We will also offer the participant breaks if needed. Though

we will not provide feedback on performance (as tests are not conducted by clinical neuropsychologists), for participants who indicate questions or concerns on their performance we will recommend they follow-up with their healthcare provider.

Justification: Administration of these measures are needed to understand the potential cognitive benefits of exercise.

One-on-one Interview. First, we will pilot test an interview guide on 2-3 PWH at UW and UCD-AMC and revise it accordingly. A final guide will be used to direct subsequent interviews consistently at both sites. The interviews will take place in a secure, private location. Questions will address the participants' perceptions of exercise; experiences with HIIT, CME, or resistance training; the coaching intervention; and what they think will help them sustain PA over the long-term. Interviews will take ~ 30 minutes, be audio-recorded, and transcribed verbatim. Dr. Webel has over 15years of experience designing, implementing, and analyzing data from qualitative studies and has successfully trained and managed qualitative data collectors across sites, obtaining high-quality data[160,161]. The interviews will be conducted in a quiet, private clinic room or conference room. Additional interviews (optional) will be conducted among participants who opt not to enroll after initially contacting the team with interest, or who decide to withdraw from the study after enrollment.

Risk: The main risk with the discussion is confidentiality or discomfort by the participant in interacting one-on-one with the interviewer.

Plan to minimize risk: Participation within the interviews will be entirely voluntary. All data will be collected using unique patient identification codes. Participant interviews will be conducted by an investigator familiar with qualitative interviews. The conversation will focus on the exercise intervention and no personal questions that might make the participant feel uncomfortable.

Justification: The goal of the Aim 3 mixed-methods analysis to fully describe and compare the perceptions of HIIT, CME, and effect of the coaching intervention to enhance self-directed PA in PWH. The addition of qualitative methods will provide insight into the aspects of health and wellness that are most valued by persons who are aging with HIV infection. The addition of the qualitative interviews allow each participant the opportunity to share his/her personal experiences.

Text Messaging Intervention.

Risk: Based on our previous work using daily electronic data collection, adverse events (AEs) due to text messaging are not expected, and no dangers to participants are expected beyond those that may be encountered in everyday life. As part of their standard medical care participants already receive many different messages about their adherence behavior that may be phrased in many different ways, with no standardization in message framing across providers. None of the tailored messages to be delivered in this study are considered any more risky or potentially harmful than other messages about adherence participants might receive during their standard medical care for HIV (where adherence is frequently a topic of discussion between clinicians and patients), and this study's messages have the advantage of being pre-validated by experts for appropriateness and factual accuracy. Therefore, the tailored messaging intervention itself is not expected to create any special risk that participants would not already encounter in the course of receiving typical medical services for HIV. Confidentiality is also a concern, and discussed below.

Plans to minimize risk: All data collected over the Internet from participants' smartphones will be completely de-identified and not traceable to the individual completing the survey; survey data transmitted over the Internet will be identified with a smartphone device ID that is not meaningful outside the context of this study, will be transmitted using a secure Internet connection (https://) via RedCap. These surveys will ask about fatigue and physical activity, and will not inquire about anything HIV related.

Expected Benefits. Participants may benefit from improved exercise adherence if the intervention is successful. The knowledge to be gained from this study is important for developing better tailored interventions that can be widely and cheaply delivered via smartphones to help people improve their adherence to exercise, treatment for HIV or other chronic diseases.

MRI/MRS Scan:

Risks: Participants may develop claustrophobia in the magnet or mild muscle cramping during the exercise portion.

Plan to minimize risk: Participants will be asked about claustrophobia during prescreening and given the option to proceed with consenting, with the recognition that they will have an MRI later. Participants will also be asked about implantable

devices or shrapnel. We do not administer contrast (gadolinium) thus further decreasing potential risks. Testing will be stopped at participant request.

Justification: PWH may have unique mechanisms underlying skeletal muscle dysfunction and physical function impairment both at baseline and in response to exercise. Leveraging the infrastructure of our existing randomized controlled trial of HIIT vs CME, we will explore the effects of 16 weeks of supervised exercise training on skeletal muscle fat (Aim 1) and *in vitro* mitochondrial function using ^{31}P-MRS (Aim 2). We will integrate the hemodynamic and metabolic responses during a single bout of exercise (before versus after training) using Co-I Dr. Englund's *v*PIVOT MRI sequence[57], which simultaneously evaluates both temporal and spatial tissue-level changes noninvasively and without use of contrast (Aim 3). Through a comprehensive evaluation of these imaging modalities with HIV, exercise type, chronic training, and the relationships with physical function changes, we can identify potential pathways to maximize exercise response, particularly among individuals who fail to reverse physical function impairments with exercise alone. Future interventional trials could augment the effects of exercise with therapy to decrease intramuscular fat (such as tesamorelin[58], semaglutide[59]), improve oxidative capacity (intermittent fasting[60]), or increase blood flow (statins[61]) to maximize function and response to exercise.

Neuroimaging (MRI) UAB ONLY:

Risks: People with claustrophobia may be uncomfortable in the scanner. The MRI machine may also be loud and cause discomfort. MRI is not safe for people with certain conditions such as pregnancy or implanted metal in the body.

Plans to minimize risk: We will carefully screen participants prior to doing the MRI to ensure the procedure is safe for them. Specifically, we will exclude those with claustrophobia, those who are pregnant (confirmed via pregnancy test on site), and those who have any implanted devices (e.g., pacemaker, insulin pumps), or embedded metal in the body (dental work is OK). Participants will also be provided with ear plugs to help increase comfort. Not being able to do the MRI will not affect participation in the other parts of the study, and the participant will be compensated if they attempt the MRI but cannot finish.

Justification: As this is an exploratory aim, we have elected to conduct the neuroMRI at only 2 time points at only one site of this study, under the supervision of a Co-I who is an expert in this technique. The potential risks are unlikely to occur, as we screen for these risk factors and will not scan those with these risk factors. The scientific justification is that understanding the underlying brain impacts of two different types of exercise is significant as it will allow for developing the most effective interventions to prevent or reverse cognitive impairment.

Muscle Ultrasound:

Risks: There is minimal risk from the muscle ultrasound assessment. Participants may experience slight pressure from the probe over the muscles or experience a cold sensation during application of gel on the skin. It is rare to experience adverse skin reactions from ultrasound gel.

Plans to minimize the risk: Participation in the muscle ultrasound portion will be voluntary. Participants will be asked if they have ever experienced adverse skin reactions to gels previously. If skin rash or reaction develops, the ultrasound will be terminated. The imaging will be stopped upon patient request.

Justification: Muscle ultrasound imaging is a clinically feasible, noninvasive technique that will allow us to estimate lean muscle mass (quantity) and fatty infiltrate of the muscle or myosteatosis (quality). Given the prevalence of decreased muscle quantity and quality in PWH, muscle ultrasounds can be used as a tool to assess the response of the muscle to 16-weeks of exercise training and compare exercise type (HIIT vs CME) by leveraging the existing infrastructure of the HEALTH study. Although exercise has been shown to improve muscle mass and quality in older adults, those with increased myosteatosis may see a blunted response to exercise interventions[177]. Utilizing muscle ultrasound imaging will allow us to assess the heterogeneity of exercise response by providing insight into specific characteristics of individuals who are "non-responders" to the exercise program.

Confidentiality and privacy: Risks will be minimized by not including personal identifying information on the forms, when possible, and by conducting interviews and collection of personal information in a private setting. Text messaging will only be related to exercise, with no mention as to HIV or other clinical conditions. All data will be collected using unique patient identification codes. All laboratory specimens, evaluation forms, reports, and other records will be identified by a coded number to maintain participant confidentiality. All records will be stored in a locked file cabinet. Study data from both sites will be collected and managed using REDCap (Research Electronic Data Capture). REDCap is a secure web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). The system was developed by a multi-institutional consortium which includes University of Colorado–Denver and Institute of Translational Health Sciences at UW and was initiated at Vanderbilt University. The database is hosted at the University of Colorado–Denver Development and Informatics Service Center (DISC), which will be used as a central location for data processing and management. While the PIs and study statistician will have access to the entire RedCAP database, we will further maintain confidentiality by limiting study staff at each site to access to their local participant data only. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the DISC. This iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap also includes a powerful tool for building and managing online surveys. The research team can create and design surveys in a web browser and engage potential respondents using a variety of notification methods. REDCap is flexible enough to be used for a variety of types of research and provides an intuitive user interface for database and survey design and data entry[7]. Lastly, clinical information will not be released without written permission of the participant, except as necessary for monitoring by the IRB or NIH.

Table 5. Sample Barriers to Exercise Adherence and Tailored Message Text

Barrier	Intervention	Sample Tailored Message
Forgetting to Exercise	*Environmental reminders.* Setting alarms or reminders helps to prompt behaviors.	"Consider setting an alarm on your watch or phone to remind you."
Competing Priorities	*"Nudge" interventions.* Small environmental changes to make the behavior more likely.	"Are there ways to add exercise to your daily activities? For instance, you could park further away from buildings to force yourself to walk."
Fatigue	*Mindfulness.* Strategies involve focused attention.	"Notice if your fatigue goes up and down over time. Does exercise make it better or worse?"
Boredom	*Environmental rewards.* Economists recommend making a reward contingent on exercising.	"Is there something like a TV program you like to watch? If you only watch it when exercising, you may want to exercise more."
Isolation/ Loneliness	*Social rewards.* Humans are social animals, and PWH have identified social barriers to exercise.	"Can you meet up with a friend to exercise, or try a sport that involves several people?"
Self-Efficacy, Environment	*Training alternate responses.* Self-efficacy increases when people have specific guidance.	"You don't have to join a gym! Here are some exercises that you can try at home …"

Overall risk associated with research visits: In this time of COVID-19, the risk of exposure is decreasing but still present. We will take all precautions per the current hospital guidelines for the prevention of COVID. Participants will be questioned as to any symptoms prior to and upon arrival to a visit. Any participants that develop COVID-19 while on study will be excluded from study visits until no longer a risk to participants and staff, with specific, updated plans detailed in the MOPS. Any participant interested in enrolling will only be eligible at least 30 days after resolution of symptoms (including fatigue, fevers, cough, etc). Any participants that have COVID-19 during the study will not be allowed to return to the research center for at least 2-4 weeks after diagnosis and resolution of symptoms.

E. Potential Scientific Problems:

We considered giving all participants the text messaging intervention and evaluating it using a quasi-experimental pre-post design. However, given that there are few evidence-based strategies to support long-term, self-directed exercise, we decided to test this effect using the most rigorous design available- a randomized clinical trial. This will allow us to assess causality and enable us to make clinical recommendations at the conclusion of this study. Although initially concerned about requiring older PWH to have cellphones, our recent work found that 85% of PWH have a cell phone (mean age 52 years) and that all send texts daily[175]. These data, coupled with data from co-I Cook indicating equally high use of cell phone and texts at UCD-AMC[176], suggest minimal impact of this criterion. Further, use of this coaching intervention is congruent with the recent NIH initiative (PA18-347) to stimulate biobehavioral and technological interventions to improve the health of vulnerable populations. Fasted samples will be banked at weeks 0 and 16 for future analyses, including assessment of inflammatory markers, myokines, metabolomics, proteomics, or transcriptomics, pending our initial analyses and the state of the science.

F. Data Analysis Plan:

Statistical Considerations. We hypothesize that among older PWH, HIIT will lead to better physical function and reduced fatigue through improvements in mitochondrial bioenergetics compared with CME.

Sample Size Calculations: We assume a 1:1 randomization to HIIT or CME balanced by site, sex (≥25% women) and age category (50-59, 60-69, and 70+) with a conservative 20% dropout rate, resulting in 40 evaluable participants/group. The second randomization at week 16 and will also be balanced by initial randomization (2x2 factorial design). Aim 1 and 2 power calculations assume two-sided, 2-sample/paired *t*-tests for between/within group comparisons of the change from baseline with a 0.05 significance level. We assume conservative within subject correlations (rho) of 0.7 or 0.5 to estimate the standard deviation (SD) of the outcome change, larger correlations and repeated measures will result in additional power. The Aim 1 primary outcome is change in 400-MWT. We assume an effect size comparable to Toohey[163], an intervention comparing HIIT to CME among middle-aged (mean age 51, SD 12 years) cancer survivors that resulted in a mean (SD) difference of 97 (82) and 36 (68) meters in 6-minute walk distance among HIIT and CME, respectively. Using rho=0.7, and a sample size of 40/group, we will have >88% power to detect a comparable *between* group differences of 45 (38) and 20 (38) second improvement in 400-MWT in HIIT and CME, respectively. For reference, in our prior exercise study[23], PWH had a 25 second improvement in 400-MWT. This also provides >99% and >81% power to detect *within* group differences in the HIIT and CME arms. For morning and evening fatigue, we assume a baseline mean of 19(8) and 27(8) points, respectively (Webel, unpublished data). With rho=0.5, and a sample size of 40/group, we will have >80% to detect a change of ≥27% and ≥20%, respectively. The primary Aim 2 outcome is change in State 3 respiration. Based on Robinson[164], we estimate a baseline mean (SD) of 580 (180) pmol O_2/min/mL using rho=0.5. This provides >81% power to detect a difference in the change of 50% (HIIT) and 30% (CME). The muscle substudy is considered exploratory, however, we anticipate adequate power. Using preliminary data, combining HEALTH+ exercise groups (N=24), provides >80% power to detect a change of -8.7% in MRI-PDFF of HEALTH+ participants. For within exercise group (CME or HIIT) comparisons, a sample size of 12 provides >80% power to detect a difference of -12.5%. For the CME versus HIIT change from baseline comparison, a sample size of 12 per group provides >80% power to detect group differences of 9.8%. For the change in OxPhos, combining HEALTH+ exercise groups (N=24, 3 dropouts/group), provides >80% power to detect an OxPhos change of 0.039. For within exercise group (CME or HIIT) comparisons, a sample size of 12 provides >80% power to detect an OxPhos difference of 0.055. For the CME verses HIIT change from baseline comparison, a sample size of 12 per group provides >80% power to detect group OxPhos differences of 0.056. For the change in aim 3, combining HEALTH+ exercise groups, a sample size of N=24 (3 dropouts/ group), provides >80% power to detect a 21% $\dot{V}O_2$ change in HEALTH+ participants. For within exercise group (CME or HIIT) comparisons, a sample size of 12 provides >80% power to detect 33% change in $\dot{V}O_2$. For the CME verses HIIT change from baseline comparison, a sample size of 12 per group provides >80% power to detect a 30% difference in the 16-week change from baseline.

Missing Data: Efforts to minimize loss to follow-up will be implemented. However, as in any longitudinal study, it is anticipated that some participants may withdraw consent, or be lost to follow-up prior to the end of the study and will have missing outcomes. To deal with missing data, a thorough investigation of the mechanisms for missing data will be conducted. For outcomes measured repeatedly over time, mixed models, sensitivity analysis will include multiple imputation [15]. Once missing values have been imputed, each multiply-imputed data set can be analyzed using standard complete-data. Final parameter estimates and their standard errors will be calculated using Rubin's formula for combining results from multiply imputed datasets [15, 16]. We will analyze our data and report final study results with and without employing the multiple imputation strategy and carefully examine and describe any discrepancies found. Finally, given the potential for non-ignorable dropout, we will accommodate dropout using a semi-parametric varying-coefficient model approach [17, 18]. The primary analyses will assume that the slope beyond dropout is linear with sensitivity analyses utilizing a slope is attenuated by 50% and a zero slope beyond dropout, the latter being similar to a last value carried forward. A sensitivity analysis using only data from completers will be conducted.

Rigor and Reproducibility. The proposed study has many features that will allow for robust and unbiased methodology, analysis, and reporting of results. These include: 1) A randomized clinical trial design minimizing potential confounding variables; 2) Standardized training, certification, and re-training of study staff collecting data and delivering the HIIT, CME, and coaching interventions (see intervention fidelity section, above); 3) Enrolling a diverse sample with an estimated sample sized based on preliminary data; 4) Collecting data on the number, reasons, and demographic characteristics from study participation refusals to assess the potential impact of unmeasured confounding variables; 5) Blinding the study staff assessing physical function and fatigue to the participants' intervention group; 6) Lab personnel analyzing the mitochondrial bioenergetics data will also be blinded to intervention group; 7) Generating regular data reports to identify any missing data early so it can be obtained, if possible; 8) Testing *a priori* hypotheses, based on our preliminary data, on

relationships between exercise intensity, physical function, and patient-reported fatigue; 9) Conducting assessments for each participant on the same equipment at each site (i.e.,VO_2, DXA, exercise equipment).

Analysis Approaches

Analysis Plan:

Aims 1 and 2: Baseline (week 0) characteristics will be compared between groups prior to comparisons of endpoints, with log transformation for normality, as appropriate. Age, sex, baseline CD4 count and/or VACS score, smoking, exercise intensity and body mass index (BMI) will be considered for inclusion into regression models; although if matching and/or balance by age and sex is achieved, these will be precision variables, rather than confounders. Differences in response by antiretroviral therapy (ART) class; prior ART exposure to zidovudine, stavudine, didanosine; use of statin; psychiatric medication burden; and use of hormone replacement therapy will also be explored. Given repeated measurements, a linear mixed effects model will be used with change from week 0 as the primary outcome.

Aim 3: Quantitative data will be summarized and used to describe physical activity (PA) amount and mode and then categorize the sample (see below for synthesis of data). After redacting identifying information, verbatim transcriptions of interviews will be entered into Dedoose [19], a secure, cloud-based qualitative analysis program. Our quality assurance protocol will include checking 25% of the transcripts to verify accuracy of the transcriptions and double-coding 10% of the transcripts to ensure inter-coder reliability of 80% or greater.[20] Under MPI Webel's direction, all responses will be analyzed using standard qualitative analytic techniques: identification of themes; coding of participants' responses by these themes performed independently by two team members (who have graduate-level training in qualitative coding); resolution of any coding discrepancies will be done by a third team member[21]. To ensure consistency, a codebook will be developed to create universal definitions for each code. The codebook will contain all codes, their definition, and exemplar quotes and will be iteratively tested until all coders agree it captures the breadth and depth of the perceptions about HIIT, CME, the coaching intervention, and sustaining long-term PA in PHW. We will search for *a priori* codes that describe the perceptions of HIIT and CME and long-term PA maintenance based initially on our literature review. Significant inductive (emerging) codes will also be identified. Coded items will be grouped together into distinct themes. Group analysis meetings will be held to compare independently-developed codes for similarity and further direction [22-24].This data reduction method, encompassing a team-based analysis, creates a robust iterative process through which the data are thoroughly discussed and analytical consensus achieved.

Synthesis of quantitative and qualitative methods*:* The goal of the Aim 3 mixed-methods analysis to fully describe and compare the perceptions of HIIT, CME, and effect of the coaching intervention to enhance self-directed PA in PWH. Our synthesis will use the qualitative data from 40 PWH to confirm quantitative findings and provide depth to our comparisons between HIIT vs CME (and coaching vs control) groups, and ultimately to identify factors that will enhance targeted interventions to help sustain long-term, self-directed PA in this population. To accomplish this, we will apply quantitative qualifiers to qualitative data to help fully understand the data. We will quantitatively categorize those in the HIIT and CME group, by sex, and self-directed exercise habit. We will visually depict these data using tools available in Dedoose and create a summary table with the following columns organized by coaching vs control and HIIT vs CME groups: Participants whose exercise (a) was maintained at 28 weeks, (b) declined after the supervised intervention but who still exercised, (c) stopped 16 weeks, with the following rows: (i) perceptions supporting exercise habits, (ii) perceptions of challenges to developing exercise habits, (iii) data explaining how the interventions affected exercise habits, and (iv) additional themes or patterns that emerge inductively from the data.

MRI/MRS Substudy: The primary endpoint will be change from baseline to 16 weeks in the endpoints defined above. Within and between group differences by CME and HIIT will be secondary.. Baseline (week 0) characteristics will be compared between groups prior to comparisons of endpoints, with log transformation for normality or non-parametric tests, as appropriate. Chi-square and Fisher's exact tests will be utilized for categorical comparisons. Paired and two-sample t-tests or non-parametric alternatives will be utilized for continuous outcomes. Pearson and/or Spearman correlations will be used to examine linear and/or monotonic associations. Linear regression models will also be utilized to separately examine the effects of age, sex or gender, race/ethnicity, smoking, other substance use, history of thymidine analogue, current ART, time since HIV diagnosis, duration ART, nadir CD4, diabetes, history of COVID-19, use of statin or metformin (or other diabetes medications), and body mass index (BMI). Stratified analyses by sex will explore potential sex-related differences. Secondary analyses and analyses of additional endpoints will be considered exploratory and complementary, respectively, with no adjustment for multiple comparisons.

Cognitive Substudy Statistical Analysis. Co-I Li (Biostatistician) will lead the analysis using R, SAS, and Mplus for repeated-measures analysis using mixed-effects modeling, a.k.a. hierarchical linear modeling or multilevel modeling. We

will examine potential group (and site) differences in demographics and health and baseline measures with two-sample t test (or Wilcoxon), ANOVA (or Kruskal-Wallis test) or Chi-square test where appropriate. Variables that differ by group will be adjusted in sensitivity analyses. We will conduct primary analyses under an intention-to-treat principle (all participants analyzed based on randomized conditions). The impact of any missing data will be mitigated by the use of mixed effects modeling with baseline covariates that are conceptually relevant and associated to consistency in data collection. In the presence of missing data, mixed effects models are fitted with all available data and provide unbiased estimates of model parameters, as long as the data are missing at random or conditionally at random (conditional on the covariates). If appropriate, we will employ imputation techniques. False discovery rate (FDR) will be used to justify multiple comparison. All tests will be two sided.

Our primary aim is to determine the efficacy of HIIT vs CME on improving cognitive function over time. In stage 1 (baseline to 4 months), a general linear mixed model with participant ID as random effect: score = Group +Time + Group*Time + Site will be used first to examine whether there is a significant group difference, wherein the study site is controlled to adjust for potential site effects. The best model fit with Bayesian information criterion (BIC) will determine the variance-covariance structure in above model. The significant interaction term in above model indicates a significant difference between two trajectories/slopes, i.e., treatment effect. The group comparison on the mean changes will also be contrasted with t test for effect size. In stage 2 (4 to 7 months), a similar general linear mixed model will applied: score = Group1 (HIIT vs CME) + Group2 (Coaching vs Control) +Group1*Group2 + Time + Group1*Time + Group2*Time + Group1*Group2*Time + Site, where the time is from 4 to 7 months. The non-significant interaction terms will be removed from the final model. Given any potential group differences in demographics and health at baseline, a sensitivity analysis will be conducted including those unbalanced variables in above models.

For exploratory analysis, sex-by-group interaction and/or race-by-group interaction will be included in above models to explore the potentially moderating effects, conducted according to the rigorous methods proposed by Hayes178. Given significant treatment effects on cognitive function, a PATH analysis will be conducted to explore the potential mediation effects of biomarker changes on cognitive function. We will also examine whether changes in parent R01 outcomes (e.g., VO2, physical function, fatigue) mediate cognitive changes. The exploratory blood markers will be obtained at baseline, 4- and 12 months, while the MRI neuroimaging markers will be obtained at the UAB site at baseline and 4 months. The group difference of biomarkers will be evaluated using a similar linear mixed regression model: scores = Group + Time + Group*Time, where the group difference on slopes and mean changes will be contrasted.

Our secondary aim is to examine psychological MoA of adherence to habitual PA at 12 months. We will examine distal predictors (i.e., sociodemographics, physical health, intervention type [HIIT vs CME and coaching vs control], changes in parent R01 outcomes [e.g., weight loss, physical function, fatigue] using laboratory and survey data, and proximal psychological predictors using EMA (e.g., self-efficacy, perceived benefits, motivation, social support). First, we will use a linear mixed regression with random intercept: PA = Predictor + Time + Predictor*Time + Site, to examine the association between PA adherence and each of the predictors of interest, adjusting for study site. Secondly, we will conduct a multiple linear mixed regression with random intercept and all significant predictors detected above as fixed effects to examine the covariate-adjusted association between PA and predictors: PA = Time + Predictor1 + Predictor2 + … + Site. The time-by-predictor interactions will be evaluated and removed from the model if not significant. The variance-covariance structure (e.g., AR1) in above models will be determined by the best model fit measured by Bayesian information criterion (BIC).

For EMA data, a linear mixed regression model including random effects for subject and day (within-subject) to account for the multilevel structure of the data will be used to examine the time-lagged effects of MoA variables occurring during a specified time interval (T−1) on PA during the subsequent (lagged) time interval (T) within each day of monitoring: PA(T) = MoA(T-1) + Time of Day + Day + site + covariates. The time interval T can be time of day or different days, for example we can use the MoA in Day 1 to predict the PA in Day 2 or use the MoA in the morning to predict the PA later in the same day. The covariates include significant distal predictors. Moderating effects will be explored by including interaction terms in above model. Concurrent effects of these MoA variables on PA (i.e., both the predictor and outcome were assessed during the same time interval) will also be examined. To explore whether the MoA variables mediate intervention (HIIT vs CME and coaching texting vs control) effects on PA, mediation analyses with focus on effect estimation rather than hypothesis testing will be conducted using path analysis with methods considering the multi-level nature of data and robust to non-normality (e.g., cluster bootstrapping), assuming a causal chain of the form: Intervention (HIIT vs CME) --> effect on MoA [as mediator] --> effect on PA. Using the estimated path coefficients, direct, indirect, and total effects will be estimated and uncertainty on these estimates be estimated computed in the form of confidence intervals. Using similar mediation approaches, we will also examine whether cognitive differences between groups at 12 months are mediated by differences in PA adherence at 12 months.

Quantitative feasibility, acceptability, and intervention fidelity outcomes will be compared across sites and exercise type using analysis of variance or chi-square tests when applicable.

Qualitative analysis will be conducted for acceptability questions at 4 months and PA barriers and facilitators at 12 months. Webel and Wheeler have a history of designing and analyzing data from qualitative studies179-181. Content analysis will be used to derive themes related to barriers and facilitators to long-term PA, which will be synthesized with quantitative data to examine correlates (e.g., demographics, health).

G. Summarize Knowledge to be Gained:

This proposal addresses important questions with individual and public health relevance and is supported by a strong interdisciplinary team of investigators with a history of successful collaboration, and the resources to implement the proposed work. This proposal will provide precise, causal data on the clinical and translational effects of two promising exercise interventions that vary by intensity and interval in a representative sample of older PWH. These data have tremendous potential to impact care for the up to 50% of PWH with physical function impairments and prevalent and burdensome fatigue. If our hypotheses are confirmed, future work will include an implementation science study, harnessing networks such as the AIDS Clinical Trials Group, of which Dr. Erlandson is an active investigator, to roll-out larger scale trials in diverse settings where PWH receive care. Thus, the proposed study is likely to stimulate additional novel and significant research that will have far-reaching impact on the health and quality of life of older PWH.

STUDY TIMELINE

We propose a 5-year timeline to accomplish our specific aims (**Table 1**). By conducting a rigorous, prospective, randomized clinical trial testing two exercise regimens, we will overcome limitations of previous studies investigating non-pharmacological approaches to improving the *healthspan* of people living with HIV. This design enables us to characterize the clinical (i.e., physical function and patient-reported fatigue) and translational (i.e., mitochondrial bioenergetics) effects of these interventions in an understudied, yet growing, population. To ensure that we meet enrollment and data collection milestones, we anticipate 4.5 full years of research procedures, with the remaining 6 months to finalize data analyses and disseminate the final study results.

R01 Cognitive substudy (HEALTH-COG) will leverage newly enrolled participants at the two sites of the parent HEALTH study (R01AG066562), add a University of Alabama at Birmingham (UAB) site, add new measures (psychological mechanisms of adherence, cognitive function, biomarkers) and a 12 month follow-up. This study is optional (to UCD/UW participants) and open to anyone enrolled in the parent HEALTH study. The sub-study R01 proposes to enroll/randomize 110 participants (UAB=60, University of Washington (UW)/University of Colorado Denver (UCD)=50 total between the two sites). Based on current enrollment numbers at the parent study sites (UCD=37 and UW=31), we anticipate it will be feasible for the new R01 to enroll the remaining participants across both sites (~32 participants), and due to timing of funding in relation to enrollment at UCD and UW, approximately 8-10 additional participants at both UCD and UW will need to enroll to meet and overall goal of 110 in this sub-study. The parent study end date is ~2 years into new R01 (yielding 2-3 additional years of study).

Table 1.

Timing (Year/Month)		Enrollment Target	Milestones
Year 1	JIT		• Protocol & Manual of procedures finalized • IRB approvals • Hospital/research center approvals • Data transfer agreements between UCD-AMC and UWfinalized and executed
	3		• Recruitment: Pre-screen potential participants, contact participants from database, advertisements/brochures in local clinics, provider meetings, presentations to community groups about study • Develop database and forms • Colorado site meeting with all investigators • Coordinate laboratory techniques between sites
	6	Begins	• **Enrollment begins** with goal of recruiting 2-3/month over 36 months

			• Monthly team meetings: review study progress, exercise session logs documenting progression, events (weekly PI/RA calls)
	9	9	• Prepare/submit Year 1 progress report & IRB continuing review • Revisit enrollment progress and recruiting strategies; readdress as needed
	12	18	• **First participant completes the study** • Prepare/meet with safety officer for q6 month review (after first patient enrolled) • Yearly site visit at Colorado
Year 2	15	27	• Enrollment, study visits continue
	18	36	• Q6 month DSMB meeting
	21	45	• Prepare/submit Year 2 progress report & IRB continuing review
	24	54	• Q6 month DSMB meeting • Yearly site visit at Colorado • Revisit enrollment progress and recruiting strategies, readdress as needed
Year 3	27	63	• Enrollment, study visits continue
	30	72	• Q6 month DSMB meeting
	33	81	• Prepare/submit Year 3 progress report & IRB continue review
	36	90	• Q6 month DSMB meeting • Yearly site visit at Colorado
Year 4	39	95	• Enrollment, study visits continue
	42	100	• Q6 month DSMB r meeting • Final participant enrolls
	45	105	• Prepare/submit Year 4 progress report & IRB continue review
	48	110	• Q6 month DSMB r meeting • Ship samples to Colorado for mitochondrial activity/content
Year 5	51	115	• **Last participant completes all study procedures** • Data cleaned, code transcripts for Aim 3, data analyses for Aim 1, begin Aim 2; submit manuscript • Dissemination of results
	54	120	• Mitochondrial activity/content analyses completed • Data analyses, coding continues
	57		• Data analyses completed for Aim 2 and start Aim 3; dissemination results • Prepare/submit IRB continuing review to complete data analyses
	60		• Study completed, results disseminated to the research and participant community

Table 1b. Participant Enrollment Goals for Each Year of the 28-week Intervention for R01 Cognitive Sub study UAB Site

		YEAR 1				**YEAR 2**				**YEAR 3**				**YEAR 4**				**YEAR 5**			
		6/1/23—3/31/24				**4/1/24—3/31/25**				**4/1/25—3/31/26**				**4/1/26—3/31/27**				**4/1/27—3/31/28**			
Project Task	**Qtr**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Target Enrollment (UAB)*				**5**	**10**	**15**	**20**	**25**	**30**	**35**	**40**	**45**	**50**	**55**	**60**						
Target UW/UCD participants for cognitive testing*†		**10**	**20**	**30**	**40**	**50**															

Note. *numbers are cumulative; †UCD/UW combined N=50 assumes leveraging ~30 participants and enrolling ~10 additional HEALTH participants at UCD and UW. **Parent study end date is ~2 years into new R01.**

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