

Official Title:

Relationship of Exercise, Sleep, and Inflammation Markers in People Living With HIV

NCT number:

NCT04946994

Document Date:

March 14, 2024

COMIRB Protocol

COLORADO MULTIPLE INSTITUTIONAL REVIEW BOARD
CAMPUS BOX F-490 TELEPHONE: 303-724-1055 Fax: 303-724-0990

Protocol #: 19-1985

Project Title: HEALTH nested Sleep Study

Principal Investigator: Christine Horvat Davey

Version Date: 03/14/2024

I. Hypotheses and Specific Aims:

The purpose of the study is to characterize the effects of two exercise interventions, high-intensity interval training (HIIT) and continuous moderate-intensity exercise (CME), on sleep and inflammation in older PWH. We propose the following aims: AIM 1. Compare the effectiveness of HIIT and CME exercise interventions on sleep in older PWH. AIM 2. Quantify inflammation markers associated with sleep quality (self-report surveys) in older PWH at baseline, between (week 8) and after exercise interventions (HIIT and CME) (week 16).

II. Background and Significance:

An estimated 50% of people living with HIV (**PWH**) in the United States are 50 years and older. Although HIV antiretroviral therapy is effective, older PWH are diagnosed with comorbidities at an earlier age,¹ which contributes to poorer health outcomes, including poor sleep quality². Up to 75% of PWH experience sleep deficiencies including poor sleep quality, insomnia, and daytime sleepiness.² Poor sleep quality leads to poor outcomes, including limited mobility,^{3,4} decrease in performance of daily activities,² and increased mortality.⁵ Sleep hygiene habits (i.e. bedroom environment, sleep schedule, caffeine) can impact sleep quality, but limited evidence exists regarding sleep hygiene habits in PWH.^{13,14} *Sleep quality is a modifiable behavior in PWH.*

Higher levels of systemic inflammation markers, CRP and interleukin (IL)-6, are associated with poor sleep quality in the general population as well as PWH.^{11,13} Systemic inflammation markers such as IL-10, IL-13, IFN- γ , and TNF- α are associated with sleep disturbance in PWH,¹⁴⁻¹⁶ while CRP, TNF- α , IL-1 β , IL-6, and IL-13 are associated with impaired sleep quality in other chronically ill populations.^{17,18} Less physical activity is also associated with increased inflammation.⁶ The collective or interacting impact of low levels of physical activity and inflammation on poor sleep quality may be stronger than either independent factor;^{6,8} therefore, it is vital to examine the potentially causal pathway between physical activity, sleep, and inflammation in order to help mitigate poor sleep quality.

Regular exercise is known to improve sleep quality and reduce inflammation across populations.¹² Continuous moderate-intensity exercise (**CME**) and high-intensity resistance exercise improves sleep quality in older adults⁹. CME with moderate-intensity resistance exercise improves physical function in older PWH, with additional improvements from higher-intensity continuous aerobic exercise with resistance exercise.¹⁰ Most exercise studies incorporate CME in which aerobic exercise is performed at 70%-75% of maximal heart rate (HR_{max}) continuously for a specified duration (i.e., a 30-min walk). An alternative, promising exercise is high-intensity interval training (**HIIT**), which uses repeated alternating short bouts of high-intensity (i.e., 80%- 95% HR_{max}) and lower intensity aerobic exercise (i.e., 60% HR_{max}). HIIT is safe and has higher efficacy in improving health outcomes compared to CME in those with chronic illness (i.e., coronary

artery disease, diabetes),^{11,12} yet little is known about the effects of HIIT on sleep in people living with HIV.¹³

The effect of HIIT on sleep quality in older PWH has not been studied. The significance and premise of the study aims are summarized in **Table 1**. Since PWH have poorer cardiorespiratory capacity (i.e., VO_{2peak} , peak oxygen consumption) compared to age-matched HIV-uninfected controls, it is vital to evaluate training interventions such as HIIT.³ To guide the dose of exercise needed to attain the maximal benefit on sleep in older PWH, we will compare changes in sleep quality and inflammation levels in response to two exercise regimens that vary by levels of intensity, HIIT and CME.

Table 1: Scientific Premise Justification	
Scientific Premise of Aims: PWH ≥ 50 years of age will achieve better sleep quality (actigraphy and self-report) and decreased inflammation with HIIT compared to CME.	
Supporting Evidence for the Premise	Extension of Evidence With This Study
Regular physical activity is linked with improved sleep quality (actigraphy and self-report). ^{12,30} (2)	Our study will examine HIIT and CME in relation to sleep quality in PWH.
Physical inactivity and poor sleep quality are linked with increased inflammation. ¹⁵ (3)	Our study will examine sleep quality and HIIT and CME in relation to inflammation markers in PWH.

III. Preliminary Studies/Progress Report:

The premise of this research proposal is the direct result of preliminary works which found that increased cardiorespiratory fitness was associated with decreased fatigue, but not depressive symptoms in PWH.¹⁹ The results indicated that interventions that improve cardiorespiratory fitness, such as physical activity, are likely to improve symptoms (e.g., fatigue, sleep quality) in PWH. Although ours was the first study to examine cardiorespiratory mechanisms associated with fatigue and depression over time in PWH, we did not collect information on sleep quality or inflammation. We further found that a greater amount of home-based physical activity was associated with reduced fatigue and an associated increase in quality of life in PWH.²⁰ In another study, we found improvement in total sleep time and efficiency in PWH that participated in a higher intensity exercise (not HIIT) program compared to CME.²¹ Although there was a small effect, it suggests that a high-intensity intervention may be needed. The present study will have an increased sample size and use a higher intensity exercise intervention (HIIT) compared to CME, which we hypothesize will lead to a greater improvement in sleep quality in PWH. The present study will evaluate and compare the effects of exercise interventions (HIIT and CME) on subjective and objective sleep quality and inflammation in older PWH. In combination, these preliminary studies demonstrate the need to investigate physical activity interventions to mitigate symptoms in PWH.

IV. Research Methods

A. Outcome Measure(s):

Primary Outcome Measures

1. Change in Sleep quality and patterns of sleep from week 0-16.
2. Change in inflammation markers from week 0-8 and 0-16.

Data collection includes wrist actigraphy, sleep survey and diary administration, and blood samples.

Actiwatch: Participants will be instructed on proper use of the actigraph (ActiGraph wGT3X-BT) and be asked to wear the device for 10 consecutive days at baseline and again post 16-week intervention.³⁷ Sleep quality and duration will be measured objectively using wrist actigraphy (ActiGraph wGT3X-BT). The actigraph device, which resembles a wristwatch, is worn on the wrist. It contains an accelerometer that detects movement from which sleep/wake states can be determined using a validated algorithm. The actigraph is able to detect light and determine when the actigraph is being worn, in order to distinguish between sleep and off-wrist time. Participants will also be instructed to complete a corresponding 10 day sleep diary that will collect information on the time each participant went to bed, wake time, time out of bed, how many times they awoke during the night, and naps taken during the day. This information will be used to score the actigraph data to determine our sleep quality primary outcome. *Our primary sleep quality outcomes will be the sleep fragmentation index, sleep efficiency, and mean sleep duration for sleep quantity.* All three will be based on actigraphy and are widely used and validated measures of sleep quality and duration.^{37,38} Secondary analyses may incorporate nap data into these three measures if naps occur regularly. Collected data will include weekday and weekend days in the 10 day period of time, and we will consider additional analyses separating weekend and weekday sleep data if needed.

Sleep Diary: While wearing the actiwatch, participants will be instructed to complete a corresponding **10 day sleep diary** that will collect information including time each participant went to bed, wake time, time out of bed, how many times they awoke during the night, and naps taken during the day. This information will be used to score the actiwatch data to determine our primary outcome, sleep quality. Collected data will include weekday and weekend days in the 10day period of time. Participants should be instructed to wear the actiwatch for 10 days, 24hours per day, except when bathing or swimming.

Sleep Surveys: Sleep quality and patterns of sleep will be evaluated using the validated Pittsburgh Sleep Quality Index (PSQI) and PROMIS Short Form –Sleep Disturbance. The PSQI measures seven domains of sleep: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the last month. The PROMIS Short Form –Sleep Disturbance measures sleep disturbance during the past week. The PSQI demonstrates reliability and validity in individuals with AIDS⁸ with a Cronbach's alpha of 0.83 and construct validity.²² The PSQI measures seven domains of sleep: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the last month. We will use the recommended scoring procedures to obtain a global score^F.²²⁻²⁴ The PROMIS Short Form – Sleep Disturbance demonstrates reliability and validity in PWH with a Cronbach's alpha of 0.87 and construct validity.^{25,26} The PSQI measures sleep quality during the past month, the PROMIS Short Form – Sleep Disturbance measures sleep disturbance during the past week, and the sleep diary will provide daily sleep data for 10 days.

Blood Draw: The primary inflammation markers of interest are IL-6, IL-10, IL-13, IFN- γ , CRP and TNF- α due to prior association with sleep quality, other inflammation markers, IL-1 β , IL-2, IL-4, IL-8 and IL-12p70 will be exploratory to identify potential pathways of sleep impairments.

B. Description of Population to be Enrolled:

The study will involve the recruitment and retention of 75 PWH from the University of Washington and the University of Colorado Denver. A total of 75 participants will be recruited during a 21-month period. This study is optional and is open to anyone enrolled in the HEALTH (R01AG066562) parent study at the University of Washington or the University of Colorado Denver. The research assistant (RA) at the University of Washington or the University of Colorado Denver will approach the potential participant already enrolled in the HEALTH-HIV study at the University of Washington or the University of Colorado Denver, explain the study purpose and procedures, and ask if that individual would like to participate. If so, the RA will take the potential participant to a private research space, review the informed consent document and enroll the participant. We will track refusals, reasons, and demographic characteristics of those refusing to participate, and examine those data as part of our ongoing data safety and monitoring activities.

The proposed study will leverage the HEALTH-HIV study infrastructure, (R01AG066562; MPI Webel and Erlandson). HEALTH-HIV is a 16-week random control trial examining the effects of HIIT and CME on physical function and fatigue, the bioenergetics mechanisms underlying these interventions in older PWH at the University of Washington and University of Colorado Denver. This study will enroll participants enrolled in the HEALTH-HIV parent study at the University of Washington and the University of Colorado Denver. The screening eligibility for the HEALTH-HIV study includes:

	Inclusion Criteria
1.	confirmed HIV infection
2.	sedentary lifestyle, defined as self-reported physical activity that breaks a sweat <3 days/week, with no regular resistance exercise for 3 months prior to the study
3.	on a current, modern ART (anti-retroviral regimen)
4.	documented HIV-1 RNA <200 copies/mL in the past 12 months
5.	willing to engage in a supervised exercise program 3 times/week for 16 weeks
6.	women must be post-menopausal due to potential confounding effects based on the skeletal muscle evaluation in the parent HEALTH-HIV study
7.	poor sleep quality based on self-report survey (Pittsburgh Sleep Quality Index, total score >5)
8.	aged ≥ 50 years
9.	English speaking
	Exclusion Criteria
1.	not controlled 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
2.	Indicators of 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
3.	New York Heart Association Class III or IV congestive heart failure, clinically significant aortic stenosis, uncontrolled angina, or uncontrolled arrhythmia

4.	Pulmonary disease- requiring the use of supplemental oxygen at rest or with physical exertion
5.	Malignancy requiring chemotherapy or radiation therapy- within 24 weeks prior to enrollment
6.	Poorly controlled diabetes- as evidenced by hemoglobin A1c > 8.5, documented within 6 months of study visit
7.	Surgery/trauma/injury/fracture- within 24 weeks prior to enrollment that may impact a subject's baseline functional testing and ability to exercise
8.	Balance impairments- that may impact functional testing and ability to safely exercise. Balance impairments will be assessed prior to enrollment into the study based on self-report and medical record.
9.	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)
10.	Use of hormonal therapy- except for replacement for documented hormonal deficiencies or for therapy among transgender individuals
11.	Active substance abuse- or other factors that could prevent compliance or safety with study visits, at the discretion of the PI

C. Study Design and Research Methods

The proposed study will leverage the HEALTH-HIV study infrastructure, (R01AG066562; MPI Webel and Erlandson). The proposed study is distinct from this study, as our study will add a characterization of the effects of exercise interventions on sleep and inflammation to the HEALTH-HIV study. The study will include five visits, including three blood draws.

Initial Screening Visit (aligns with parent study, screening visit #2): Consent, actiwatch initiation, sleep diary and sleep survey administration.

Consent: The RA at the University of Washington or the University of Colorado Denver will approach the potential participant already enrolled in the HEALTH-HIV study at the University of Washington or the University of Colorado Denver, explain the study purpose and procedures, and ask if that individual would like to participate. If so, the RA will take the potential participant to a private research space, review the informed consent document (see procedures, below), and enroll the participant. After obtaining informed consent, the first of two baseline visits will include Respironics actiwatch initiation, provide sleep diary and sleep survey administration (Pittsburgh Sleep Quality Index (PSQI) and PROMIS Short Form –Sleep Disturbance). Please note, the medical history, PSQI and PROMIS SF are already collected as part of the ongoing HEALTH study.

Actiwatch Initiation and Sleep Diary: The RA will initialize the participant's actiwatch and instruct each participant on proper use of the actiwatch (Phillips Respironics Actiwatch Spectrum Plus). During initialization the RA will enter all required demographic information. If a participant is transgender, sex assigned at birth should be used, as the variable of sex does not impact the data. Participants will be asked to wear the device for 10 consecutive days at baseline and again post 16-week intervention. The actiwatch, which resembles a wristwatch and is worn on the non-dominant wrist. The device should be fully charged. While wearing the actiwatch, participants will be instructed to complete a corresponding **10 day sleep diary** that will collect information including time each

participant went to bed, wake time, time out of bed, how many times they awoke during the night, and naps taken during the day. This information will be used to score the actiwatch data to determine our primary outcome, sleep quality. Actiwatch Event Marker: Subjects should be instructed to press the event marker when turning off lights and tv and attempting to go to sleep for the evening (“lights out”), and then again when getting out of bed for the final time in the morning. This should occur each day. The event marker is the small button located on the left side of the watch. The button must be pressed for 3+ seconds, until the time display blinks “---“for a few seconds before returning to the original time display. Research staff should demonstrate what this looks like. Stress the importance of using the event marker, as it will help with data editing later on. NOTE: The “---“ line will only appear on the screen when the event marker is pushed after the watch has begun collecting data. Collected data will include weekday and weekend days in the 10 day period of time. Participants should be instructed to wear the actiwatch for 10 days, 24hours per day, except when bathing or swimming. RA’s will contact the participant’s midweek to see if they have any questions.

Sleep Surveys: Sleep quality and patterns of sleep will be evaluated using the validated Pittsburgh Sleep Quality Index (PSQI) and PROMIS Short Form –Sleep Disturbance. The PSQI measures seven domains of sleep: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the last month. The PROMIS Short Form –Sleep Disturbance measures sleep disturbance during the past week. The PSQI demonstrates reliability and validity in individuals with AIDS⁸ with a Cronbach’s alpha of 0.83 and construct validity.²² The PSQI measures seven domains of sleep: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the last month. We will use the recommended scoring procedures to obtain a global score^{F.22-24} The PROMIS Short Form – Sleep Disturbance demonstrates reliability and validity in PWH with a Cronbach’s alpha of 0.87 and construct validity.^{25,26} The PSQI measures sleep quality during the past month, the PROMIS Short Form – Sleep Disturbance measures sleep disturbance during the past week, and the sleep diary will provide daily sleep data for 10 days.

Screening Visit #2 (aligns with parent study, screening visit #3): Fasting blood draw after refraining from exercise for ≥ 48 hours, return actiwatch and sleep diary, and sleep survey administration.

Blood Draw: A fasting blood draw will be taken at the beginning of the second baseline visit, collected between 6:30 – 10:00 am. The participant should refrain from exercise for ≥ 48 hours. The clinical blood draw should include:

- 10 ml K2EDTA tube (plasma will be collected for analysis for inflammatory markers)

The primary inflammation markers of interest are IL-6, IL-10, IL-13, IFN- γ , CRP and TNF- α due to prior association with sleep quality, other inflammation markers, IL-1 β , IL-2, IL-4, IL-8 and IL-12p70 will be exploratory to identify potential pathways of sleep impairments.

Return of actiwatch and sleep diary: The RA will collect the actiwatch and sleep diary from the participant. The RA will check wear time for the actiwatch. If the participant did

not meet wear time criteria (wearing the device for seven days), the RA will ask the participant if they are willing to wear the device again for approximately seven days. If they are willing to re-wear the device, the participant should be reinstructed on proper use and wear time criteria and provide the participant with a new sleep diary. The RA should also check the sleep diary for completeness. If the participant did not complete or has missing data in the diary the RA should assist the participant with completion of any missing data, if possible.

Sleep Surveys: The Pittsburgh Sleep Quality Index (PSQI) and PROMIS Short Form – Sleep Disturbance forms should be completed to measure sleep quality and patterns of sleep.

Intervention Week 8 Visit (aligns with parent study, part one of intervention week 8 study visit): Fasting blood draw after refraining from exercise for ≥ 48 hours and sleep surveys. The procedures are described above.

Intervention Week 16 Visit (aligns with parent study, part one of intervention week 16 study visit): Fasting blood draw after refraining from exercise for ≥ 48 hours, actiwatch initiation, sleep diary and sleep survey administration. The procedures are described above.

End of Study Visit (aligns with parent study, end of part one study visit): Return actiwatch and sleep diary. The procedures are described above.

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

Potential risks: The potential risks of this study are those associated with blood draws and privacy.

Venipuncture: There is a small risk of local hematoma or infection associated with blood sampling. On rare occasions, drawing blood can cause dizziness, presyncope, and even syncope. Measures taken to minimize these risks are detailed below.

Confidentiality and privacy: The use of questionnaires and collection of personal medical information poses a risk to confidentiality and privacy and may cause embarrassment. Measures taken to minimize these risks are detailed below.

Adequacy of Protection against Risks

Recruitment and informed consent: The recruitment strategies are detailed in Recruitment/Retention Strategies. Participants from the University of Washington or the University of Colorado Denver sites of the parent study HEALTH-HIV that have consented to being contacted in the future for new research studies will be proactively recruited, through methods approved by the IRB (phone, email, or communication through the electronic medical record). If the participants are interested in the study, a brief phone screen and medical record review will be conducted to ensure eligibility and the participant will be scheduled for consenting. Prior to implementation, the study and its consent form will be approved by the University of Washington IRB. The consenting process is part of the initial study visit and will take via phone or in-person. Participants are either sent a

copy of the consent form in advance or are given one at the start of the visit; time is allowed for review of the consent form. Participants discuss with member of the research team the following: a) have the study explained in detail; b) discuss their reasons and motivation for wanting to participate to determine whether they are realistic; c) discuss any practical problems (e.g., scheduling conflicts, vacations) that could interfere with participation; d) have their questions answered; and e) demonstrate their ability to provide informed consent by describing their understanding of the major study goals and what is expected of them if they choose to participate.

Participants are given a signed copy of the consent form and a signed copy is maintained in the study chart for each participant. Health Insurance Portability and Accountability Act (HIPAA) authorization is included in the consent form. The member of the research team who will obtain consent and HIPAA authorization from participants will have complied with the University of Washington and/or the University of Colorado Denver IRB and HIPAA education requirements. The PI will be responsible for ensuring that research personnel are prepared to convey information to participants specific to the study protocol. The participant is informed of the purpose of the study, potential medical and social risks of participation, their right to withdraw at any time, and compensation. If willing to participate, the participant and study member obtaining consent will sign the consent.

Protection against risk: The inclusion/exclusion criteria will assure that participants at highest risk for adverse events are excluded. In addition, the specific measures to decrease risks regarding the study procedures are detailed below:

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

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 whether in-person or by phone. Phone calls will only be related to study appointments, with no mention as to HIV. All data will be collected using unique participant 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 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 database is hosted at the University of Washington and the University of Colorado Denver, which will be used for data processing and management. 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. REDCap also includes a powerful tool for building and managing online surveys. The PI 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. Lastly, clinical information will not be released without written permission of the participant, except as necessary for monitoring by the IRB, FDA, or NIH.

E. Potential Scientific Problems:

The potential scientific problem with this study includes the potential benefits to an individual participant in the study are not known. All participants will undergo exercise training, which can trigger many beneficial adaptations, but not all individuals respond favorably with such adaptations. The potential benefits of the study to others could be considerable. If our hypotheses are true, this study will make a significant contribution towards improved sleep quality in this patient population. Poor sleep quality is associated with insomnia,^{9,10} daytime sleepiness,^{9,11} depression,^{6,7,10} and a decrease in the performance of daily activities.⁶ These data will be critical for the design of future multimodal interventional studies to evaluate interventions to improve sleep quality and achieve successful aging in persons with or without HIV infection. The information gained from this project will be applicable to PWH, and may be extrapolated to HIV-uninfected populations with chronic diseases.

F. Data Analysis Plan:

Sample size for parameter estimation. As a pilot study, our primary goal is parameter and variance estimation to inform the design of a larger subsequent trial. For Aim 1, we have >80% power to detect a difference in the decrease in poor sleep quality of 75% for HIIT participants versus a 25% decrease for CME participants, assuming a sample size of 25 per group and a significance level of 0.05. Based on previous Exercise for Healthy Aging (EHA) data,²¹ at each time point, we anticipate a margin of error of 14.4%, 2.7% and 9.2% for PSQI, SE and TST, respectively. For Aim 2, assuming a log transform for the inflammatory markers, based on previous EHA data,²¹ we anticipate a margin of error of $\pm 28.4\%$ and $\pm 50.7\%$ for change from baseline in IL-6 for the CME and HIIT groups, respectively. For the change from baseline in TFN-a, we anticipate a margin of error of $\pm 22.1\%$ and $\pm 17.4\%$ for CME and HIIT groups, respectively. As this is a pilot study, tests of CME versus HIIT and associations of inflammation with sleep quality will be conducted, but all results will be reported as hypothesis generating. As in the HEALTH-HIV study, linear, logistic and mixed effects regression models will be utilized with adjustment for baseline values, potential confounders and precision efficiency variables. Analyses will be conducted in SPSS (26) and R. Missing Data. For our longitudinal endpoints, we will implement efforts to minimize loss to follow-up. However, as in any longitudinal study, we anticipate that some patients may withdraw consent, or be lost to follow-up prior to the end of the study and will have missing data. Multiple imputation with standard errors estimated using Rubin's rules will be utilized. Given the potential for non-ignorable dropout, we will accommodate dropout using a semiparametric varying-coefficient approach.^{27,28}

Rigor and Reproducibility. The proposed study has numerous elements that will allow for unbiased and robust design, methodology, analysis, and reporting of results. These include: (1) use of standardized qualitative methods for in-depth interviews; (2) recruitment from the HEALTH-HIV study, a randomized clinical trial design minimizing potential confounding variables; (3) standardized training for interventionists providing the HIIT and CME interventions to ensure safety and fidelity of the intervention; (4) collection of participant refusal data (number, reason, and demographic characteristics) to assess for the impact of unmeasured confounding variables; (5) generation of monthly data reports to identify any missing data, so if possible, it can be acquired to minimize missing data; and (6) testing a priori hypotheses, based on the literature, on relationships between exercise, sleep quality, and inflammation markers to promote rigor of the research.

G. Summarize Knowledge to be Gained:

This proposal addresses significant questions related to the health of older PWH and has individual as well as public health relevance. We believe the proposed research represents a unique opportunity within our healthcare system to mitigate symptom burden through improved sleep quality in PWH and has the potential to significantly impact medical care of PWH.

H. References:

1. Womack, J.A., Goulet, J.L., Gibert, C., Brandt, C., Chang, C.C., Gulanski, B. Fraenkel, L., Mattocks, K., Rimland, D., Rodriguez-Barradas, M.C., Tate, J., Yin, M.T. Justice, A.C., & Veterans Aging Cohort Study Project Team. (2011). Increased risk of fragility fractures among HIV infected compared to uninfected male veterans. *PLoS One*, 6(2), e17217. <https://doi.org/10.1371/journal.pone.0017217>
2. Oursler, K. K., Goulet, J. L., Crystal, S., Justice, A. C., Crothers, K., Butt, A. A., Rodriguez-Barradas, M. C., Favors, K., Leaf, D., Katzel, L. I., & Sorkin, J. D. (2011). Association of age and comorbidity with physical function in HIV-infected and uninfected patients: results from the Veterans Aging Cohort Study. *AIDS patient care and STDs*, 25(1), 13–20. <https://doi.org/10.1089/apc.2010.0242>
3. Oursler, K.K., Sorkin, J.D., Smith, B.A., & Katzel, L.I. (2006). Reduced aerobic capacity and physical functioning in older HIV-infected men. *AIDS Research and Human Retroviruses*, 22(11), 1113-1121. <https://doi.org/10.1089/aid.2006.22.1113>
4. Richert, L., Dehail, P., Mercie, P., Dauchy, F.A., Bruyand, M., Greib, C., Dabis, F., Bonnet, F., Chene, G., & GECSA. (2011). High frequency of poor locomotor performance in HIV-infected patients. *AIDS*, 25(6), 797-805. <https://doi.org/10.1097/QAD.0b013e3283455dff>
5. Milanini, B., Catella, S., Perkovich, B., Esmaeili-Firidouni, P., Wendelken, L., Paul, R., Greene, M., Ketelle, R., & Valcour, V. (2017). Psychiatric symptom burden in older people living with HIV with and without cognitive impairment: the UCSF HIV over 60 cohort study. *AIDS care*, 29(9), 1178–1185. <https://doi.org/10.1080/09540121.2017.1281877>
6. Gutierrez, J., Tedaldi, E. M., Armon, C., Patel, V., Hart, R., & Buchacz, K. (2019). Sleep disturbances in HIV-infected patients associated with depression and high risk of obstructive sleep apnea. *SAGE open medicine*, 7, 2050312119842268. <https://doi.org/10.1177/2050312119842268>
7. Allavena, C., Guimard, T., Billaud, E., de la Tullaye, S., Reliquet, V., Pineau, S., Hüe, H., Supiot, C., Chennebault, J. M., Michau, C., Hitoto, H., Vatan, R., & Raffi, F. (2014). Prevalence and risk factors of sleep disturbances in a large HIV-infected adult population. *Journal of the International AIDS Society*, 17(4 Suppl 3), 19576. <https://doi.org/10.7448/IAS.17.4.19576>
8. Rubinstein, M.L. & Selwyn, P.A. (1998). High prevalence of insomnia in an outpatient population with HIV infection. *Journal of Acquired Immune Deficiency Syndromes*, 19(3), 260–265. <https://doi.org/10.1097/00042560-199811010-00008>
9. Santos, I.K., Azevedo, K., Melo, F.C.M., Lima, Kátia K.F., Pinto, R.S., Dantas, P.M.S. Medeiros, H.J., & Knackfuss, M.I. (2018). Lifestyle and sleep patterns among people living with and without HIV/AIDS. *Revista da Sociedade Brasileira de Medicina Tropical*, 51(4), 513-517. <https://doi.org/10.1590/0037-8682-0235-2017>
10. Crum-Cianflone, N. F., Roediger, M. P., Moore, D. J., Hale, B., Weintrob, A., Ganesan, A., Eberly, L. E., Johnson, E., Agan, B. K., & Letendre, S. (2012). Prevalence and factors associated with sleep disturbances among early-treated HIV-infected persons. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*, 54(10), 1485–1494. <https://doi.org/10.1093/cid/cis192>

11. Irwin, M. R., Olmstead, R., & Carroll, J. E. (2016). Sleep Disturbance, Sleep Duration, and Inflammation: A Systematic Review and Meta-Analysis of Cohort Studies and Experimental Sleep Deprivation. *Biological psychiatry*, 80(1), 40–52. <https://doi.org/10.1016/j.biopsych.2015.05.014>
12. Santos, R.V., Tufik, S., & De Mello, M.T. (2007). Exercise, sleep and cytokines: is there a relation? *Sleep Medicine Reviews*, 11(3), 231–239. <https://doi.org/10.1016/j.smr.2007.03.003>
13. Lee, K. A., Gay, C., Portillo, C. J., Coggins, T., Davis, H., Pullinger, C. R., & Aouizerat, B. E. (2012). Types of sleep problems in adults living with HIV/AIDS. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*, 8(1), 67–75. <https://doi.org/10.5664/jcsm.1666>
14. Reid, S., & Dwyer, J. (2005). Insomnia in HIV infection: a systematic review of prevalence, correlates, and management. *Psychosomatic medicine*, 67(2), 260–269. <https://doi.org/10.1097/01.psy.0000151771.46127.df>
15. Wirth, M. D., Jagers, J. R., Dudgeon, W. D., Hébert, J. R., Youngstedt, S. D., Blair, S. N., & Hand, G. A. (2015). Association of Markers of Inflammation with Sleep and Physical Activity Among People Living with HIV or AIDS. *AIDS and behavior*, 19(6), 1098–1107. <https://doi.org/10.1007/s10461-014-0949-y>
16. Gay, C. L., Zak, R. S., Lerdal, A., Pullinger, C. R., Aouizerat, B. E., & Lee, K. A. (2015). Cytokine polymorphisms and plasma levels are associated with sleep onset insomnia in adults living with HIV/AIDS. *Brain, Behavior, and Immunity*, 47, 58–65. doi:10.1016/j.bbi.2014.11
17. Moore, S. E., Voss, J. G., & Webel, A. R. (2020). Sex-Based Differences in Plasma Cytokine Concentrations and Sleep Disturbance Relationships Among People Living With HIV. *The Journal of the Association of Nurses in AIDS Care : JANAC*, 31(2), 249–254. <https://doi.org/10.1097/JNC.000000000000125>
18. Erlandson, K. M., Wilson, M. P., MaWhinney, S., Rapaport, E., Liu, J., Wilson, C. C., Rahkola, J. T., Janoff, E. N., Brown, T. T., Campbell, T. B., & Jankowski, C. M. (2020). The Impact of Moderate or High-Intensity Combined Exercise on Systemic Inflammation among Older Persons with and without HIV. *The Journal of infectious diseases*, jiaa494. Advance online publication. <https://doi.org/10.1093/infdis/jiaa494>
19. Horvat Davey, C., Perazzo, J. D., Vest, M., Josephson, R. A., & Webel, A.R. (2019). The Impact of Cardiorespiratory Function on Fatigue and Depression in PLHIV. *AIDS Care*, 1-5. <https://doi.org/10.1080/09540121.2019.1659920>
20. Webel, A. R., Perazzo, J., Decker, M., Horvat-Davey, C., Sattar, A., & Voss, J. (2016). Physical activity is associated with reduced fatigue in adults living with HIV/AIDS. *Journal of advanced nursing*, 72(12), 3104–3112. <https://doi.org/10.1111/jan.13084>
21. Hixon, B., Burgess, H.j., Wilson, M.P., MaWhinney, S., Jankowski, C., & Erlandson, K. (Under review). A Supervised Exercise Intervention Fails to Improve Subjective and Objective Sleep Measures Among Older Adults with and without HIV.
22. Beck, S. L., Schwartz, A. L., Towsley, G., Dudley, W., & Barsevick, A. (2004). Psychometric evaluation of the Pittsburgh Sleep Quality Index in cancer patients. *Journal of pain and symptom management*, 27(2), 140–148. <https://doi.org/10.1016/j.jpainsymman.2003.12.002>
23. Buysse, D.J., Reynolds III, C.F., Monk, T.H., Berman, S.R., & Kupfer, D.J. (1989). The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Journal of Psychiatric Research*, 28(2), 193–213. [https://doi.org/10.1016/0165-1781\(89\)90047-4](https://doi.org/10.1016/0165-1781(89)90047-4)

24. Alessi, C.A., Martin, J.L., Webber, A.P., Alam, T., Littner, M.R., Harker, J.O., & Josephson, K.R. (2008). More daytime sleeping predicts less functional recovery among older people undergoing inpatient post-acute rehabilitation. *Sleep*, 31(9), 1291-1300.
25. Evon, D. M., Amador, J., Stewart, P., Reeve, B. B., Lok, A. S., Sterling, R. K., Di Bisceglie, A. M., Reau, N., Serper, M., Sarkar, S., Lim, J. K., Golin, C. E., & Fried, M. W. (2018). Psychometric properties of the PROMIS short form measures in a U.S. cohort of 961 patients with chronic hepatitis C prescribed direct acting antiviral therapy. *Alimentary pharmacology & therapeutics*, 47(7), 1001–1011. <https://doi.org/10.1111/apt.14531>
26. Schnall, R., Liu, J., Cho, H., Hirshfield, S., Siegel, K., & Olender, S. (2017). A Health-Related Quality-of-Life Measure for Use in Patients with HIV: A Validation Study. *AIDS Patient Care STDS*, 31(2), 43-48. <https://doi.10.1089/apc.2016.0252>
27. Forster JE, MaWhinney S, Ball EL, Fairclough D. A varying-coefficient method for analyzing longitudinal clinical trials data with nonignorable dropout. *Contemporary Clinical Trials*. 2012;33(2):378-385.174.
28. Moore CM, MaWhinney S, Forster JE, et al. Accounting for dropout reason in longitudinal studies with nonignorable dropout. *Statistical Methods Medical Research*. 2017;26(4):1854-1866.