NCT04889521

Title of Study: Impact of Distal Sensory Polyneuropathy on Function in Persons Living with HIV and a Pilot Study of Mindfulness Meditation and Transcutaneous Nerve Stimulation (TENS) in Persons Living with HIV-related Peripheral Neuropathy Document

Date: 3.18.2024 (PROTOCOL)

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INTERVENTIONAL RESEARCH PROTOCOL TEMPLATE

(HRP-503a)

STUDY INFORMATION

- **Title of Project:** Impact of Distal Sensory Polyneuropathy on Function in Persons Living with HIV and a Pilot Study of Mindfulness Meditation and Transcutaneous Nerve Stimulation (TENS) in Persons Living with HIV-related Peripheral Neuropathy
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- **Protocol Version and Date:** v10.0 3.1.2024

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Approval Date: 3/18/2024
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1.0 Research Design

1.1 Purpose/Specific Aims

The overall goal of this study is to explore the impact of HIV-associated distal sensory polyneuropathy on function, physical activity and pain pressure threshold, and conduct an interventional pilot trial of mindfulness meditation and transcutaneous nerve stimulation (TENS) to

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mitigate symptoms and improve function in persons living with HIV-related distal sensory neuropathy (DSP).

A. Objectives

Aim 1. Determine if the presence of painful distal sensory polyneuropathy in the feet adversely affects function (gait and physical performance), physical activity, and pain pressure threshold in persons living with HIV (PLHIV). (From this point forward, protocol related to Aim 1 will be referred to as "cross-sectional phase")

Aim 2. Determine the feasibility and effects of (1) mindfulness meditation or (2) transcutaneous nerve stimulation (TENS) on clinical and functional outcomes in persons with HIV-associated painful distal sensory polyneuropathy in the feet. (From this point forward, protocol related to Aim 1 will be referred to as "interventional phase")

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B. Hypotheses / Research Question(s)

Hypothesis for Aim 1 (cross-sectional phase): Temporal and spatial characteristics of gait, walking endurance, physical performance scores and pain pressure threshold scores will be worse, and physical activity will be lower, in those with DSP than in those without DSP.

Hypothesis for Aim 2 (interventional phase): There will be a beneficial effect on all clinical and functional outcomes in each of the 2 intervention groups (mindfulness meditation; TENS) compared to a standard care group.

1.2 Research Significance

Anti-retroviral therapy (ART) has increased longevity of PLHIV. However, comorbidities and disability may emerge over time.[1-3] Chronic pain is common, with prevalence of 39-85%.[4-10] Chronic pain in PLHIV has a multifactorial etiology.[11,12] It is associated with increased odds of impaired mobility, self-care, usual activities, and disability.[13-16] In middle aged and older PLHIV, pain is associated with frailty.[17,18]

Distal sensory polyneuropathy (DSP) is a common neurological complication of HIV disease, with prevalence exceeding 40%.[19-21] The etiology is related to HIV-infection, associated metabolic changes, mitochondrial dysfunction, and neurotoxic effects of ART.[20,22-24] Risk factors include older age, lower CD4 nadir, and exposure to certain antiretroviral drugs.[20,25-27] Symptoms include impaired sensation, paresthesia, diminished reflexes, and pain. In PLHIV and DSP, the prevalence of chronic neuropathic pain is 54-78%.[25,28-30] We have found that DSP is associated with worse quality of life, poorer lower extremity function, and more severe disability,[14,31] and that disability associated with DSP in PLHIV is mediated through pain and depression.[32] Other studies have reported associations between DSP and sleep disturbance, interference with activities and emotions, and greater levels of catastrophizing and depression.[33-35] Although impairments of gait and balance have been identified in PLHIV[36], it remains unclear if DSP further affects gait and physical performance.

Management of pain in PLHIV and DSP can include pharmaceutical approaches[37], but their effectiveness is uncertain.[38] Opioids have poor efficacy for management of chronic pain.[39] The literature on non-pharmaceutical management of DSP in PLHIV is limited to 2 trials of night splints[40] and exercise[41] and a small number of pilot or case studies that have explored yoga, electrical stimulation, or a combination of manual therapy, electrical stimulation, stretching, and self-management.[42-45]

Mindfulness meditation has been used to reduce stress and symptoms in people with chronic diseases, including HIV.[46] The practice involves bringing one's attention to experiences in the present moment.[47] Mindfulness has been shown to reduce ART side-effects, enhance quality of life, improve emotional status, and improve CD4 cell count in PLHIV.[48-51] It has not been specifically studied for management of chronic pain in PLHIV and DSP.

Conventional TENS involves low-voltage current applied to the skin for pain relief.[52] High frequency TENS is recommended for patients who are taking opioid pain medication.[53] TENS has been widely studied in patients with chronic pain, although its effectiveness remains uncertain.[54,55] In patients with

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diabetic neuropathy, studies have reported that TENS is effective for reduction in neuropathic symptoms.[56] Other than a double case study using micro-current TENS (a specific form that is not widely used)[43], TENS has not been studied in PLHIV and DSP.

DSP is associated with a wide array of impairments and limitations in PLHIV, but the study of non-pharmaceutical intervention strategies has been sparse. Mindfulness mediation and conventional TENS have not been studied in this population. Current gaps in knowledge include quantification of whether DSP in PLHIV adversely affects gait, balance, physical performance, and physical activity, and identification of interventions to improve clinical outcomes.

1.3 Research Design and Methods

This study will include a cross-sectional phase for Aim 1, and an interventional phase with 3 arms for Aim 2. All enrolled participants (those with DSP and those without DSP) will be involved with the cross-sectional phase for Aim 1. Only participants with DSP and foot pain will continue on into the interventional phase for Aim 2. Data will be collected via an array of non-invasive tests and questionnaires that will be administered a members of the study team. All data except for gait and walking endurance will be collected in a private room. Gait and walking endurance measurements will be conducted in a room of adequate size for this, or in a nearby unobstructed hallway.

A. Research Procedures

Procedure (in order of occurrence)	When	Where	By Whom
Recruitment of Participants Cross-sectional phase and interventional phase	May 2022-June 2024	various HIV treatment centers in the NJ region and/or HIV support groups	Dave Kietrys Judith Barberio Shobha Swaminathan Oonagh Breen
Screening for Eligibility Cross-sectional phase and interventional phase	May 2022–June 2024	By phone or HIPAA compliant ZOOM meeting	Dave Kietrys Oonagh Breen
Consenting Cross-sectional phase and interventional phase	May 2022–June 2024	Rutgers study site (in Newark or Voorhees) or Wm Way Center in Philadelphia	Dave Kietrys Oonagh Breen
Baseline Testing (Week 0) Cross-sectional phase and interventional phase	May 2022–June 2024	Rutgers study site (in Newark or Voorhees) or Wm Way Center in Philadelphia for in-person tests and questionnaires Physical activity monitoring done at home	Dave Kietrys Richard Ferraro Andrew Lynch Oonagh Breen
Group assignment and instruction in interventions for TENS and MM groups Interventional phase only	May 2022–June 2024	Rutgers study site (in Newark or Voorhees) or Wm Way Center in Philadelphia	Dave Kietrys Andrew Lynch Oonagh Breen
Home-based Interventions and daily	May 2022–July 2024	Participant's home	Participant

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question re: adherence via text message (6 weeks) Interventional phase only			
Post-intervention Testing (Week 7) Interventional phase only	May 2022–July 2024	Rutgers study site (in Newark or Voorhees) or Wm. Way Center in Philadelphia for in-person tests and questionnaires Physical activity monitoring done at home	Dave Kietrys Richard Ferraro Andrew Lynch Oonagh Breen
Follow up Questionnaire (Week 15) Interventional Phase only for those who were in TENS or MM groups and enrolled after IRB approval to add follow up questionnaire.	April 2024 – Sept. 2024	Paticipant's home or location of choice via Email/RedCap	David Kietrys

Procedures to monitor subjects for safety and minimize risk of harm during testing: Study staff will follow CDC and Rutgers COVID precautions that are in place at the time (such as wearing a face mask and a face shield) throughout the testing session. Study staff will wash their hands before and after a testing session and sanitize their hands frequently throughout a testing session. All equipment including pens or iPads used for questionnaires will be disinfected both prior to and immediately following a testing session for a given participant. Participants will be scheduled one at a time with no overlap. If more than one participant is scheduled on the same day, there will be a full hour gap between participants to allow time for disinfection of all testing equipment. Participants' appointments will be postponed if they are experiencing symptoms of COVID-19 or are febrile or had a high risk exposure to a COVID infected individual during the week prior to their testing appointment. This will be determined by the PI or study staff calling the participant the day prior to or the morning of their appointment. Prior to testing procedures, participants' resting heart rate, blood pressure, respiratory rate and temperature will be taken. If vital signs values or temperature are outside of acceptable ranges, testing will not proceed on that date. All participants will be required to follow COVID precautions that are in place at the time of testing throughout the testing session. Currently, this includes participants wearing masks throughout the session, sanitizing their hands with hand sanitizer prior to the start of testing and prior to leaving the testing session, and maintaining social distance of at least 6' between study team personnel and participants will be maintained except for when testing procedures require closer proximity. All participants will be guided by and supervised by a study team member throughout all testing procedures. During the balance tests that are included the Short Physical Performance Battery, the PI or his designated study team member will stand adjacent to the participant and provide guarding in case the participants experience a loss of balance. The other test that will require proximity of less than 6' is pain pressure threshold testing. After each test, participants will be asked if they would like to sit and rest before continuing on to the next test. If participants appear to be in any distress or become lightheaded during testing, they will be given the option of lying down on a treatment table or sitting in a chair, and their vital signs will be reassessed.

Procedures to monitor subjects for safety and minimize risk of harm during the period of home-based interventions: Participants in the interventional phase will be notified on baseline testing day that they should contact the PI if any problems arise during the 6 week at-home

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intervention period. Participants in the TENS will be educated on how to inspect their skin after removing electrodes following a TENS treatment. Because DSP typically causes impaired sensation in the distal extremities TENS electrodes will not be placed on the feet. Rather, the locations will be more proximal at designated points on the lower extremities that have been assessed (on the day of baseline testing) by study personnel to have protective sensation as assessed with a 5.07 gauge (10 gram) Semmes-Weinstein monofilament. Participants in the TENS group who do not have protective sensation over the TENS sites in the legs will NOT be provided with TENS treatment. In addition, participants will be contacted once a week by text message meeting and will be asked if they are experiencing any problems of difficulties with the home-based interventions.

Randomization: The cross-sectional phase does not require randomization. For the interventional phase, participants with DSP will be randomly assigned to either the TENS group or the MM group or the standard care group (SC) using a web-based random number generator (https://www.randomizer.org/) that will link a group code (TENS, MM, or SC) to a participant's study ID number. Once a participant has been randomized to a group, the matching of the participant's ID number and assigned group will be delivered a study team member in a sealed opaque envelope.

B. Data Points

Data elements include an array of non-invasive physical performance tests, physical activity monitoring, pain pressure threshold testing, and questionnaires. See Section 1.6 B. for detail on dependent variables/outcome measures.

The data elements will be collected at baseline (Week 0) for all participants.

At Week 0, all participants complete a demographic and health questionnaire and a physical activity questionnaire, the Brief Pain Inventory, and will undergo testing related to gait, walking endurance, physical performance, and pain-pressure threshold. They will receive a physical activity monitor that they will be asked to wear for 5 days and then ship back to the PI in a pre-paid shipping box.

Those with DSP-related pain will also complete questionnaires for pain, quality of life, depression and anxiety, catastrophizing behavior, and resilience at Week 0.

Those participants with DSP-related pain will be randomized to continue on to the interventional phase. Throughout the 6-week intervention period, participants in the TENS and MM groups will receive a daily text message in the morning that will ask them if they completed the home-based treatment on the day prior, and a weekly text message to ask if any problems have emerged; participants in the standard care group will receive a weekly text message to ask if any problems have emerged. All participants in the interventional phase will return for follow up testing after 6 weeks of intervention (Week 7), at which time all measurements taken at Week 0 will be repeated. In addition, participants will complete a satisfaction questionnaire at Week 7. They will once again receive a physical activity monitor that they will be asked to wear for 5 days and then ship back to the PI in a pre-paid shipping box. In addition, those who were randomized to the TENS or MM groups starting in March 2024 will complete a short follow up questionnaire at Week 15.

C. Study Duration

72-80 participants will be seen one time for testing, followed by 5 days of physical activity monitoring for the cross-sectional phase.

The 36-40 participants without DSP will be engage for approximately one week (baseline testing followed by 5 days of activity monitoring).

The 36-40 participants with DSP-related pain will continue with the interventional phase for 6 weeks (home-based treatment or usual care/control) then return for post-intervention testing at week 7, followed by 5 days of activity monitoring. At week 15, those who were randomized to the

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TENS or MM groups will receive a short follow-up questionnaire via email/RedCap. Overall, those with DSP (interventional phase) will be participating for approximately 8 weeks if in the Usual Care Group, or 15 weeks if in the TENS or MM groups (to account for the follow up questionnaire).

The overall duration of the study is expected to be 12 months. Participants will be enrolled on a rolling basis as determined by their available for test dates and times.

D. Endpoints

Study end point for those participants without DSP (cross-sectional phase only) will be 5 days after the date of a participant's on-site baseline testing. (Following on-site baseline testing, they will continue to wear an activity monitor for 5 days). Study end point for those participants with DSP and randomized to the Usual Care group will be approximately 8 weeks from the date of on-site baseline testing, allowing for 5 days of activity monitoring after on-site base line testing, 6 weeks of home based intervention, on-site post-intervention testing, and 5 days of activity monitoring after the on-site post-intervention testing. Study end point for those participants with DSP and randomized to the TENS or MM groups will be approximately 15 weeks from the date of on-site baseline testing, allowing for 5 days of activity monitoring after on-site base line testing, 6 weeks of home based intervention, on-site post-intervention testing, 5 days of activity monitoring after the on-site post-intervention testing, and finally a follow up questionnaire at week 15. All test procedures are expected to safe. However, any participants who report increase physical or emotional distress during testing will be invited to rest so that study staff can reassess their vital signs and determine if the participant can continue if they choose to do so. Testing procedures will cease if a participant falls or sustains any form of injury during the testing.
Although the interventions (TENS, mindfulness meditation) pose negligible risk, if a participant experiences a serious adverse event, that participant will be withdrawn from the study. Any adverse events will be reported to the IRB. Furthermore, participants can elect to withdraw themselves from the study at any time.

1.4 Preliminary Data

There is no preliminary data; this is a new study. This interventional phase of this study will be used to generate data on the feasibility and effect sizes of the interventions that will be used for future projects.

1.5 Sample Size Justification

A sample of 80 participants will be enrolled in the cross sectional phase and 40 participants (those with DSP) will continue on to the interventional phase.
The target sample size of 72 (36 with DSP and 36 without DSP) for the cross sectional phase is adequate to explore of between group differences in gait, physical performance, physical activity, and pain pressure threshold variables. For the interventional phase, 36 participants (12 participants in each of the 3 groups) is adequate to demonstrate feasibility and determine effect sizes that can inform a future randomized controlled trial. The expected accrual rate is 90% (drop-out rate of <10%); thus, the number enrolled will be 80.

1.6 Study Variables

A. Independent Variables, Interventions, or Predictor Variables

For the cross-sectional phase of the study, gait, physical performance, physical activity, pain severity, pain interference, and pain pressure threshold will be compared between those that have painful distal sensory polyneuropathy and those who do not. See 1.6 B. for a detailed list of variables.
The interventional phase will include 3 treatment groups: transcutaneous nerve stimulation (TENS), mindfulness meditation (MM), and a standard care group (SC). TENS and MM will involve commonly used standards and are not experimental.

TENS: TENS settings (frequency, pulse width, and mode) will be set by the investigator prior to giving the unit to the participants. Participants in the TENS group will receive a new battery-operated hand-held TENS300 device (TENSpros.com, St. Louis, MO), 6 sets of electrodes

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(TENSpros.com, St. Louis, MO), six 9-volt batteries, and an instruction manual. After the 5th day of baseline physical activity monitoring, they will be provided with a link to a 10-minute instructional video. A dual channel setup will be utilized to deliver one channel to each lower extremity at sites proximal to the feet that have been determined to have protective sensation with at 5.07 gauge (10 gram) Semmes-Weinstein monofilament. Standard settings for chronic pain will be used. Patients will be instructed in how to apply 2"X2" self-adhering electrodes to the designated points on the lower extremities, how to control the intensity, and how to change the battery if needed. They will be advised to self-administer TENS once a day for 30 minutes. Instructions provided to participants will include that they should adjust the intensity of the TENS at the start of the session and again after 15 minutes, as follows: "Turn the intensity dial up to the point where the electrical stimulation feeling is unpleasant or painful, then immediately turn it down just slightly to just below that" and, "after 15 minutes, turn up the intensity dial more to point where is it unpleasant or painful, then turn it down just slightly below that". If participants lose or damage their TENS unit, it will promptly be replaced with a new unit.

Mindfulness Meditation (MM): After the 5th day of baseline physical activity monitoring, participants in the MM group will sent a link to view a 10-minute orientation video.. Participants in the MM group will be instructed to complete a 15-30-minute meditation every day. The meditations will be guided by pre-recorded audios, with a different theme each week. Participants will receive a link to the pre-recorded audios by text message and/or email.

Standard care group: Participants in the standard care group will be advised to continue with their current pain management strategies and continue to see any health care providers that they normally see. Following 5 days of activity tracing (after their return for data collection at W7), TENS and MM will be offered to them at no cost. If they accept the offer of TENS, they will receive the same equipment and instruction that was provided to those in the TENS group. If they accept the offer of MM, they will be provided with links to the orientation video and the meditation audio recordings.

B. Dependent Variables or Outcome Measures

	Type of Variable	Measurement Instrument
Cross-sectional phase Week 0 (all participants)	Temporal and spatial characteristics of gait (walking velocity; step length; step time; stride width; cadence; footfall area)	Zeno instrumented walkway with PKMAS gait analysis software (Protokinetics Inc., Havertown, PA)
	Walking endurance	6-Minute Walk Test
	Physical performance	Short Physical Performance Battery
	Whole body strength	Mid-thigh Pull test
	Pain pressure threshold	Digital Algometer (JTech Medical, Midvale, UT)
	Physical activity over 5 days Physical activity past week	Actigraph wGT3X-BT device (Actigraph, Pensacola, FL) International Physical Activity Questionnaire Short-Form (IPAQ-SF)
	Pain severity Pain interference	Brief Pain Inventory
Interventional phase Week 0 (only those participants	Quality of life	Medical Outcomes Study HIV Health Survey (MOS-HIV)

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with DSP-related pain) Note: variables measured for cross-sectional phase will also be used as outcomes for interventional phase	Depression and/or Anxiety	Hospital Anxiety and Depression Scale (HADS)
	Catastrophizing behaviors	Pain Catastrophizing Scale
	Resilience	6-item Brief Resilience Scale
	Self-reported use of pain medication	Pain management questionnaire
Interventional phase Weeks 1-6 (only those participants with DSP-related pain)	Adherence to home-intervention protocol (fidelity)	Participant responses to daily text messages
Interventional phase Week 7 (only those participants with DSP-related pain)	All variables as listed for Week 0 (including those used in cross-sectional phase)	As listed for Week 0 (including those used in cross-sectional phase)
	Satisfaction (Week 7 only)	Post-intervention Satisfaction Questionnaire
Interventional phase Week 15 (only for those participants with DSP-related pain who were randomized to the TENS or MM groups)	Ongoing use of interventions	Follow up Questionnaire

1.7 Drugs/Devices/Biologics: Not applicable

A. Drug/Device Accountability and Storage Methods: Not applicable

1.8 Specimen Collection

A. <u>Primary</u> Specimen Collection: Not applicable

B. <u>Secondary</u> Specimen Collection: Not applicable

1.9 Data Collection

A. <u>Primary</u> Data Collection

- **<u>Locations</u>**:
  - Rutgers SHP site: 200 College Drive, Jefferson Hall #317, Blackwood, NJ. This site is a lab housed in the program of the PI (Kietrys) and thus no special permission is needed.
  - Rutgers SHP site: 65 Bergen St., #214, Newark NJ. This site is a lab housed in the department of PI (Kietrys) and thus no special permission is needed.
  - William Way LGBT Community Center, Philadelphia PA
  - Jefferson Health, 400 Laurel Oak Road, Voorhees, NJ
  - Broadway House, 298 Broadway, Newark, NJ

- **<u>Process of Data Collection</u>**:

Data	How it will be collected	Who will oversee the process
Demographic and health information	Questionnaire (web-based using RedCap) Completed on-site	Dave Kietrys Rich Ferraro Andrew Lynch Oonagh Breen
Zeno instrumented walkway with PKMAS gait analysis	On-site using portable equipment (Zeno	Dave Kietrys Richard Ferraro

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software (Protokinetics Inc., Havertown, PA)	instrumented walkway) and laptop computer.	Andrew Lynch Oonagh Breen
6-Minute Walk Test	On-site using space in the lab or hallway that is clear.	Dave Kietrys Richard Ferraro Andrew Lynch Oonagh Breen
Actigraph GT3X-BT device with ActiLife software (Actigraph, Pensacola, FL)	While on–site, participant will receive instruction in use of Actigraph device. After the participant receives instruction in use of the device, they will be wear it for 5 days, then ship it back to the PI in a pre-paid shipping box. Data from the participant will be downloaded into a laptop computer before the device is wiped of date, disinfected, and prepared to use with a different participant.	Dave Kietrys
International Physical Activity Questionnaire Short-Form (IPAQ-SF)	Questionnaire (web-based using RedCap) Completed on-site	Dave Kietrys Andrew Lynch Rich Ferraro Oonagh Breen
Short Physical Performance Battery	On-site, using portable equipment (chair, stopwatch)	Dave Kietrys Richard Ferraro Andrew Lynch Oonagh Breen
Mid-thigh Pull	On-site, using portable equipment (load cell platform)	Dave Kietrys Richard Ferraro Andrew Lynch Oonagh Breen
Digital Algometer (JTech Medical, Midvale, UT)	On-site, using portable digital algometer	Dave Kietrys Richard Ferraro Andrew Lynch Oonagh Breen
Brief Pain Inventory	Questionnaire	Dave Kietrys

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	(web-based using RedCap) Completed on-site	Andrew Lynch Rich Ferraro Oonagh Breen
Medical Outcomes Study HIV Health Survey (MOS-HIV)	Questionnaire (web-based using RedCap) Completed on-site	Dave Kietrys Andrew Lynch Rich Ferraro Oonagh Breen
Hospital Depression and Anxiety Scale (HADS)	Questionnaire (web-based using RedCap) Completed on-site	Dave Kietrys Andrew Lynch Rich Ferraro Oonagh Breen
Pain Catastrophizing Scale	Questionnaire (web-based using RedCap) Completed on-site	Dave Kietrys Andrew Lynch Rich Ferraro Oonagh Breen
Pain management questionnaire	Questionnaire (web-based using RedCap) Completed on-site	Dave Kietrys Andrew Lynch Rich Ferraro Oonagh Breen
Brief Resilience Scale	Questionnaire (web-based using RedCap) Completed on-site	Dave Kietrys Andrew Lynch Rich Ferraro Oonagh Breen
Tracking of adherence to home-based treatment	Participant responses to daily text message from a study-specific Twilio account.	Dave Kietrys Andrew Lynch
Satisfaction questionnaire	Questionnaire (web-based using RedCap) Completed on-site	Dave Kietrys Andrew Lynch Rich Ferraro Oonagh Breen
Follow up questionnaire (for those who were in TENS and MM groups)	Questionnaire (web-based using RedCap) Completed at participant's home or location of their choice.	David Kietrys

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- **Timing and Frequency**:
  Cross-sectional phase: All participants will be seen individually at Week 0 (baseline) for all variables included in the cross-sectional study. In addition, participants will wear an activity monitor for 5 days following the baseline session.

  Interventional phase. Participants who continue on into the interventional phase (those with DSP) will complete additional questionnaires at Week 0 and then will be seen again at Week 7 (following 6 weeks of home-based intervention or usual care). In addition, participants will wear an activity monitor for 5 days following the Week 7 session.

  At Week 0, the expected time to complete all data collection for those participants without DSP is 45 minutes (gait and physical performance tests) and the expected time for those participants with DSP is 1.5 hours (45 minutes for gait and physical performance tests and 45 minutes for questionnaires.)
  At Week 7, the expected time to complete all data collection is 1.5 hours (45 minutes for gait and physical performance tests and 45 minutes for questionnaires.)

  At week 15, participants who were randomized to the TENS and MM groups will receive a short follow-up questionnaire (5-10 minutes to complete)

- **Procedures for Audio/Visual Recording**: Not applicable.

- **Study Instruments**:

Instrument	Details	References to support Validity and Reliability
Zeno instrumented walkway	Instrumented walkways are widely used to collect gait data. The walkway is a 15' flat mat placed on for floor. The mat is placed along the loop used for the 6-minute walk test (described below). Data from the 3 laps during the 6-minute walk test will be used. Participants are instructed to walk at their natural pace.	Vallabhajosula, et al. (2019). Concurrent validity of the Zeno walkway for measuring spatiotemporal gait parameters in older adults. *Journal of Geriatric Physical Therapy*, *42*(3), E42-E50. Lynall, R. C., Zukowski, L. A., Plummer, P., & Mihalik, J. P. (2017). Reliability and validity of the protokinetics movement analysis software in measuring center of pressure during walking. *Gait & Posture*, *52*, 308-311.
6-Minute Walk Test	A 60' loop is marked on the floor with traffic cones. Participants are instructed to walk at their natural pace. Over 6 minutes of walking, the number of completed laps are counted. A rolling measurement wheel is used to measure the distance walked during the final lap (if not full) at 6 minutes.	ATS statement: guidelines for the six-minute walk test. (2002). ATS committee on proficiency standards for clinical pulmonary function laboratories. *Am J Respir Crit Care Med, 166*(1), 111-117. Perera, S., Mody, S. H., Woodman, R. C., & Studenski, S. A. (2006). Meaningful change and responsiveness in common physical performance measures in older adults. Journal of the *American Geriatrics Society, 54*(5), 743-749..

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Actigraph wGT3X-BT device	The Actigraph device resembles a watch. It is worn around the wrist. It should be worn continuously during the prescribed 5-day period except for when it is removed for re-charging.	Acebo, C., & LeBourgeois, M. K. (2006). Actigraphy. *Respiratory Care Clinics of North America, 12*(1), 23-30. Aadland, E., & Ylvisåker, E. (2015). Reliability of the Actigraph GT3X+ accelerometer in adults under free-living conditions. *PloS One, 10*(8), e0134606.
International Physical Activity Questionnaire Short-Form (IPAQ-SF)	Questionnaire, self-report estimate of physical activity over past 7 days	Lee, P. H., Macfarlane, D. J., Lam, T. H., & Stewart, S. M. (2011). Validity of the international physical activity questionnaire short form (IPAQ-SF): A systematic review. *International journal of behavioral nutrition and physical activity*, *8*(1), 1-11. Craig, C., Marshall, A., Sjostrom, M., Bauman, A., Lee, P., Macfarlane, D., ... & Stewart, S. (2017). International physical activity questionnaire-short form. *J Am Coll Health*, *65*(7), 492-501.
Short Physical Performance Battery (SPPB)	The SPPB includes 3 tests: Balance tests that involved timed standing (up to 10 sec. each) in side-by-side standing, semi-tandem standing and tandem standing. Gait speed over a 4-meter distance is calculated. Timed 5 time-sit-to-stand test. The participant rises from sitting a chair 5 times.	Mijnarends, D. M., Meijers, J. M., Halfens, R. J., ter Borg, S., Luiking, Y. C., Verlaan, S., ... & Schols, J. M. (2013). Validity and reliability of tools to measure muscle mass, strength, and physical performance in community-dwelling older people: a systematic review. *Journal of the American Medical Directors Association, 14*(3), 170-178. Westman, A. W., Combs-Miller, S., Moore, J., & Ehrlich-Jones, L. (2019). Measurement characteristics and clinical utility of the short physical performance battery among community-dwelling older adults. *Archives of Physical Medicine and Rehabilitation, 100*(1), 185-187.
Mid-thigh Pull	The participant stands on a testing platform with hips and knees slightly bent, and holds a handle bar that is connected to the platform via a chain and linked to a force gauge. The participant is instructed to pull up on the bar with maximum effort for 5 seconds. This is repeated 3 times and the maximum value is recorded. The test serves as an indicator of total body strength.	Comfort, P., Dos' Santos, T., Beckham, G. K., Stone, M. H., Guppy, S. N., & Haff, G. G. (2019). Standardization and methodological considerations for the isometric midthigh pull. *Strength & Conditioning Journal*, *41*(2), 57-79. Brady, C. J., Harrison, A. J., & Comyns, T. M. (2018). A review of the reliability of biomechanical variables produced during the isometric mid-thigh pull and isometric squat and the reporting of normative data. *Sports Biomechanics, 19*(1), 1-25.
Digital Algometer	The blunt tip of the algometer is placed along the dorsal web-space (between 1st and 2nd toes) or the proximal	Vaughan, B., McLaughlin, P., & Gosling, C. (2007). Validity of an electronic pressure algometer. *International Journal of Osteopathic Medicine, 10*(1), 24-28.

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	lateral tibia just below the lateral tibial plateau. Pressure is slowly increased until subject reports it is painful, after which the pressure is removed. The value (threshold) is recorded.	Vaughan, B., McLaughlin, P., & Gosling, C. (2007). Validity of an electronic pressure algometer. *International Journal of Osteopathic Medicine, 10*(1), 24-28.
Brief Pain Inventory	Questionnaire, subscale scores for Pain Intensity and Pain Interference calculated based on responses to questions.	Cleeland, C. S., & Ryan, K. M. (1994). Pain assessment: Global use of the Brief Pain Inventory. *Annals Academy of Medicine, Singapore, 23*(2):129-138. Keller, S., Bann, C. M., Dodd, S. L., Schein, J., Mendoza, T. R., & Cleeland, C. S. (2004). Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. *The Clinical Journal of Pain, 20*(5), 309-318.
Medical Outcomes Study HIV Health Survey (MOS-HIV)	Questionnaire, subscale scores for Physical Quality of Life and Mental Quality of Life are calculated based on responses to questions.	Wu AW, Revicki DA, Jacobson D, Malitz FE. (1997). Evidence for reliability, validity and usefulness of the Medical Outcomes Study HIV Health Survey (MOS-HIV). *Qual Life Res, 6*(6):481-493.
Hospital Anxiety and Depression Scale (HADS)	Questionnaire, subscale scores for depression or anxiety calculated based on responses to questions.	Bjelland, I., Dahl, A. A., Haug, T. T., & Neckelmann, D. (2002). The validity of the Hospital Anxiety and Depression Scale: an updated literature review. *Journal of Psychosomatic Research*, *52*(2), 69-77. Stern, A. F. (2014). The hospital anxiety and depression scale. *Occupational Medicine*, *64*(5), 393-394.
Pain Catastrophizing Scale	Questionnaire, overall score calculated based on responses to questions.	Osman, A., Barrios, F. X., Gutierrez, P. M., Kopper, B. A., Merrifield, T., & Grittmann, L. (2000). The Pain Catastrophizing Scale: Further psychometric evaluation with adult samples. *Journal of Behavioral Medicine, 23*(4), 351-365. Osman, A., Barrios, F. X., Kopper, B. A., Hauptmann, W., Jones, J., & O'neill, E. (1997). Factor structure, reliability, and validity of the Pain Catastrophizing Scale. *Journal of Behavioral Medicine, 20*(6), 589-605.
Brief Resilience Scale	Questionnaire, overall score calculated based on responses to questions	Kyriazos, T. A., Stalikas, A., Prassa, K., Galanakis, M., Yotsidi, V., & Lakioti, A. (2018). Psychometric evidence of the Brief Resilience Scale (BRS) and modeling distinctiveness of resilience from depression and stress. *Psychology, 9*(7), 1828-1857.

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Pain management questionnaire	Questionnaire	No reliability or validity to report; questions are custom designed for this study.
Tracking of adherence to treatment	Daily question via text message	No reliability or validity to report; question is custom designed for this study.
Post-intervention Satisfaction Questionnaire	Questionnaire	No reliability or validity to report; questions are custom designed for this study.
Follow up questionnaire	Questionnaire	No reliability or validity to report; questions are custom designed for this study.

- **Ethnographic Studies, Interviews, Or Observation**: Not applicable.
- **Subject Identifiers**: No subject identifiers outside of the participant identification number will be linked to the data.

B. Secondary Data Collection: Not applicable.

1.10 Timetable/Schedule of Events

Enrollment will be done in a rolling fashion over several months. The chart below outlines the overall timetable.

Timetable	
Recruitment of Participants Cross-sectional phase and interventional phase	May 2022 – June 2024
Screening for Eligibility Cross-sectional phase and interventional phase	May 2022 – June 2024
Consenting Cross-sectional phase and interventional phase	May 2022 – June 2024
Baseline Testing (Week 0) Cross-sectional phase and interventional phase	May 2022 – June 2024
Group assignment and instruction in interventions Interventional phase only	May 2022 – June 2024
Home-based Interventions (6 week period) Interventional phase only	May 2022 – July 2024
Post-intervention Testing (Week 7) Interventional phase only	May 2022 – July 2024
Follow up questionnaire.	April 2024 – Sept. 2024
Data Analysis	Ongoing over the course of the study through Sept. 2024
Manuscript Preparation and Submission	Sept. 2024 – Jan. 2025

2.0 Project Management

2.1 Research Staff and Qualifications

Study Personnel (Role)	Credentials	Qualifications
David Kietrys (PI)	PT, PhD, FCPP	PhD from Temple University. Faculty at Rutgers School of Health Professions.

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		Prior PI and author of several studies on the topic of HIV-related disability and neuropathy. Has served as PI on several prior studies as noted on record with the Rutgers eIRB. Office located across the hall from the Blackwood study site.
Judith Barberio (Co-investigator)	PhD, RN, APN-c	Faculty at Rutgers School of Nursing. Extensive clinical and research experience in HIV. Office located in same building as Newark study site.
James Scott Parrott (Co-investigator; Statistician)	PhD	Faculty at Rutgers School of Health Professions. Statistician and co-director of Rutgers School of Health Professions Methodology and Statistics Support Team. Co-investigator along with PI on prior HIV-related studies.
Richard Ferraro (Co-investigator)	PT, PhD	Faculty at Rutgers School of Health Professions. Expertise in use of Zeno instrumented walkway and gait analysis.
Adrienne Simonds (Co-investigator)	PT, PhD	Faculty at Rutgers School of Health Professions. Research experience in chronic pain and TENS for management of chronic pain.
Oonagh Breen (Study staff)	DPT student	Student of PI; will be trained by PI in any relevant study procedures.
Shobha Swaminathan	MD, MB, BS	Associate Professor of Medicine at Rutgers New Jersey Medical School. She is the Clinical Research Site Leader for the NIH-funded clinical trials unit at NJMS. Infectious disease physician with special interest in HIV.

2.2 Research Staff Training

All persons assisting with this project have reviewed and the protocol and if appropriate based on their role, trained in study procedures by PI David Kietrys (consenting and all procedures except ZENO instrumented walkway and Mid-Thigh Pull) or Richard Ferraro (ZENO instrumented walkway and Mid-Thigh Pull). All have been debriefed in their respective roles in the study. Ongoing email communications between team members will assure fidelity to study procedures.

2.3 Resources Available

This study is funded by a $5000 grant from Rutgers Interdisciplinary Center for HIV Research (RICHR). Any over-run costs will be absorbed by the PI's discretionary account and/or by his Department. Other resources available are existing equipment in the PI's department (ZENO instrumented walkway, PKMAS gait analysis software, Mid-thigh pull testing equipment, digital algometer); the PI will have access to the equipment throughout the study. Space for consenting and data collection will be provided by the PI (Kietrys) in his program/department labs located in Blackwood NJ and Newark NJ or by the William Way Community Center. Co-investigator James Parrott is a statistician and will be supporting data analysis.

The testing and the interventions used in this study pose negligible risk to participants. However, should any need for medical or psychological support emerge, the PI (Kietrys) will make appropriate referrals for participants who sustain and injury or illness as a direct consequence of participation in the study.

2.4 Research Sites

Rutgers SHP site: 200 College Drive, Jefferson Hall #317, Blackwood, NJ.

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Rutgers SHP site, 65 Bergen St. Newark, NJ. St. Michael's Medical Center, 111 Central Ave., Newark, NJ 07102

Jefferson Health New Jersey (Kennedy Health Systems), 333 Laurel Oak Road, Voorhees, NJ 08043; 354 Hurffville-Crosskeys Road, Sewell, NJ 08080 and 80 Tanner Street, Haddonfield, NJ 08033

William Way Community Center, 1315 Spruce St., Philadelphia, PA (data collection site)

Jefferson Health, 400 Laurel Oak Road, Voorhees, NJ 08043 (data collection site)

Broadway House, 298 Broadway, Newark NJ 07104 (data collection site)

Rutgers UHosp site (office of Dr. Swaminathan), 140 Bergen St Level D, Newark, NJ 07103 (recruitment site)

3.0 Multi-Center Research

Not applicable.

4.0 Subject Considerations

4.1 Subject Selection and Enrollment Considerations

A. Method to Identify Potential Subjects

Methods to identify potential participants will be flyers at 3 HIV treatment centers known to the PI (Kietrys) and co-investigators (Barberio, Swaminathan): Jefferson Health New Jersey (in Voorhees NJ, Sewell NJ, and Haddonfield NJ) Peter Ho Memorial Clinic at St. Michaels Medical Center, 111 Central Ave, Newark NJ, and office of Dr. Swaminathan, 140 Bergen St Level D, Newark, NJ respectively. Kietrys, Barberio and Swaminathan have long standing relationships with these centers and provide care to patients at these centers. No research activities will take place at these sites. Only recruitment will take place at these sites. Medical staff at these facilities will be made aware of the study should they choose to share information about the study with their patients via flyers that are available at these facilities. The flyer for the study will be shared with HIV support groups and HIV organizations in NJ that are identified over the course of the study.

In addition, the information about the study will be sent to HIV+ adults within a 25-mile radius of Newark NJ via ResearchMatch.org (RM). A preliminary search on RM determined there are 70 HIV+ adults within a 25-mile radius of Newark NJ who are registered with RM.

Potential participants who express interest will be interviewed by phone or HIPAA compliant ZOOM meeting to determine eligibility.

B. Recruitment Details

Recruitment by Kietrys, Barberio, and Swaminathan at Jefferson Health New Jersey in Voorhees NJ, Peter Ho Memorial Clinic at St. Michaels Medical Center in Newark NJ, and office of Dr. Swaminathan, 140 Bergen St Level D, Newark, NJ will begin upon IRB approval and continue through March of 2024. Materials will consist of **flyer** that is made available to patients at these as well as other HIV treatment centers in NJ, Buddies of New Jersey, Hyacinth AIDS Foundation, and other HIV support groups and organizations in NJ that are identified over the course of the study.

Information about the study will be sent to HIV+ adults within a 25-mile radius of Newark NJ via ResearchMatch.org (RM); as per the RM process, individuals who express interest will then receive an email from PI David Kietrys with additional study information and an invitation to arrange a phone call to go over screening questions and determine eligibility.

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C. Subject Screening

Individuals will be screened for eligibility during a phone call or by HIPAA compliant ZOOM meetings by David Kietrys (PI) or Oonagh Breen (study staff). Screening will involve a series scripted questions pertaining to inclusion and exclusion criteria. Individuals will be advised upon conclusion of the call or ZOOM if they are eligible to participate in the study.

- **Inclusion Criteria**

  The inclusion criteria for all participants will be:
  - diagnosis of HIV infection currently treated with ART
  - CD4 count of at least 200 cells/mm^3
  - 18-89 years old
  - able to read and write in English
  - means to travel to a study site.

Half of the sample (those continuing on to the interventional phase) will have painful DSP in the feet. To screen for DSP, potential participants will be asked if they have been diagnosed with DSP in their feet and the Single Question Neuropathy Screen[57,58] (specifically for symptoms in the feet) will be administered. An affirmative response to either question will be used to classify them as having DSP. For those with DSP, an additional inclusion criteria are:

- average daily self-reported pain in the feet of at least 3/10 on a 0-10 numerical pain scale
- pain in the feet present for at least the past 3 months
- no changes in medications used to manage pain in the past 4 weeks
- availability of a mobile phone to receive text messages over the course of the intervention period
- for interventional phase only: no use of TENS or mindfulness meditation in the prior 6 months

- **Exclusion Criteria**

  Exclusion criteria include certain conditions as listed in the chart below.

Exclusion Criterion	Justification for Exclusion
current opportunistic infection(s)	presence suggests that the patient is severely immunocompromised and in need of medical attention
CD4 count <200 cells/mm^3	presence suggests that the patient is severely immunocompromised and in need of medical attention
dementia	patient would be unable to successfully complete questionnaires
uncontrolled psychiatric disorder	patient's behaviors and responses to questionnaires may be altered or invalid
wounds or sores on the feet	may not be safe for patient to participate with testing. wounds or sores may affect gait
musculoskeletal or neurological conditions (other than DSP) that may affect gait	Aim 1 seeks to determine how DSP affects gait, so persons with other conditions that affect gait (such as hemiplegia, amputation, multiple sclerosis, etc.) are an exclusion
pregnancy	may affect gait and other physical performance tests

For participants who have difficulty reading and comprehending the questionnaires, we will accommodate them by having a study team member read aloud each of the questions prior to asking them to enter a response.

4.2 Secondary Subjects

Not applicable.

4.3 Number of Subjects

A. Total Number of Subjects

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Number of subjects who are expected to be screened: 160
Number of subjects who are expected to be enrolled: 80
Number of subjects needed to complete the research procedures: 72

B. Total Number of Subjects If Multicenter Study

Not applicable.

C. Feasibility

Given the PI's prior experience with recruitment of HIV+ participants for prior studies, coupled with access to 3 key HIV treatment centers, it is highly feasible that the target number of participants can be recruited by March 2024. It is estimated that there are more than 37,000 PLHIV in New Jersey, and DSP is common co-morbidity in PLHIV (with prevalence exceeding 40%).

4.4 Consent Procedures

A. Consent Process

- **Location of Consent Process**
  Consent will take place at either of the 4 study sites (200 College Drive, Jefferson Hall #317, Blackwood, NJ or 65 Bergen St., Newark, NJ or Willam Way Center in Philadelpihia, PA or Broadway House in Newark NJ)
- **Ongoing Consent**
  Not applicable. This is a relatively short-term study (total time involvement for those in the interventional phase is approximately 8 weeks).
- **Individual Roles for Researchers Involved in Consent**
  David Kietrys and Oonagh Breen will be involved with consent process. Dr. Kietrys will offer to email the consent form to the potential participants prior to the date they are scheduled for baseline data collection if they wish to receive it by email and read in advance of the consenting date. Upon arrival on the date for consenting and baseline testing, Kietrys or Breen will review the consent form and answer any questions. Signed consent forms will be scanned into a separate secure password protected folder on the university servers and accessible only to appropriate project team members, after which paper copies will be shredded.
- **Consent Discussion Duration**
  It is estimated that between 10 and 15 minutes will be devoted to consent discussion. More time (up to 30 minutes) can be allotted if needed.
- **Coercion or Undue Influence**
  As part of the consent form and consent discussion, potential participants will be clearly advised (both in writing on the consent form and verbally during the discussion) that their participation is entirely voluntary and that they may withdraw from the study at any time.
- **Subject Understanding**
  The details of the study will be described to potential participants who are deemed eligible (based on the screening). Furthermore, the details of the study will be reviewed with the potential participants during the consenting discussion. Testing procedures will be summarized prior to the testing session. During tests, explicit and clear instructions regarding test procedures will be given. Those randomized to the TENS group will receive an instruction manual and a one-on-one ZOOM session to educate them on how to use TENS. For randomized to the mindfulness meditation group will watch a brief orientation video , and then receive text messages with links to the audio files the will guide the meditation. Those randomized to the standard care group will continue to see any health care providers that they normally see and continue to use any pain management strategies that they normally use. In addition, they will be offered TENS and mindfulness meditation audios upon conclusion of study. At all points along the way, participants will be given the opportunity to ask any questions that they may have.

B. Waiver or <u>Alteration</u> of Consent <u>Process</u>

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- **Waiver or Alteration Details**
  Not applicable.

- **Destruction of Identifiers**
  Not applicable, as a waiver of consent is not being requested.

- **Use of Deception/Concealment**
  Not applicable.
  a. **Minimal Risk Justification**
     The testing procedures are all non-invasive and will be closely guided and monitored by study personnel. The demands of the physical testing procedures do not exceed the demand of typical daily activity for most participants. The treatments used in this study are non-invasive, non-experimental, home-based, and are widely used in health care. Adverse side effects of the treatments used in this study are not expected.
  b. **Alternatives**
     Not applicable, as a waiver of consent is not being requested.
  c. **Subject Debriefing**
     Not applicable, as a waiver of consent is not being requested.

C. Documentation of Consent

- **Documenting Consent**
  Participants will be asked to sign a hard copy of a consent form. Thus, their consent will be documented in writing. Signed consent forms will be scanned into a separate secure password protected folder on the university servers and accessible only to appropriate project team members, after which paper copies will be shredded.
- **Waiver of Documentation Of Consent (i.e., will not obtain subject's signature)**
  Not applicable.

4.5 Special Consent/Populations

A. Minors-Subjects Who Are Not Yet Adults

- **Parental Permission**
  Not applicable as minors will not be enrolled in this study.
- **Non-Parental Permission**
  Not applicable as minors will not be enrolled in this study.
- **Assent Process**
  Not applicable as minors will not be enrolled in this study.
- **Documentation of Assent**
  Not applicable as minors will not be enrolled in this study.
- **Reaching Age of Majority During Study**
  Not applicable as minors will not be enrolled in this study.

B. Wards of the State

- **Research Outside of NJ Involving Minors**
  Not applicable as minors will not be enrolled in this study.

C. Non-English-Speaking Subjects

Not applicable. Only participants who speak, read and write in English will be enrolled.

- **Process for Non-English-Speaking Subjects**
  Not applicable.
- **Short Form Consent for Non-English Speakers**
  Not applicable.

D. Adults Unable to Consent / Decisionally Impaired Adults

Not applicable.

- **NJ Law-Assessment of Regaining the Capacity to Consent**
  Not applicable.
- **Capacity to Consent**
  Not applicable.
  a. **NJ Law-Selecting A Witness**

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Not applicable.

b. Removing a Subject

If the subject expresses dissent to continued participation, they will be withdrawn from the study.

4.6 Economic Burden and/or Compensation for Subjects

A. Expenses

The expenses incurred by participants are any expenses related to travel that exceed the $5 cash travel stipend provided on on-site testing days. Participants in the interventional phase may incur costs for mobile device data usage depending on their plan.

B. Compensation/Incentives

All participants will receive a $25 gift card and $5 cash at the time of baseline testing (W0). The participants with DSP who are continuing on to the interventional phase will receive a second $25 gift card and $5 cash at the time of post-intervention testing (W7). The sum is felt to provide a reasonable incentive. The $5 cash payment is intended to offset travel costs such as gas or bus fare.

C. Compensation Documentation

The PI (Kietrys) will maintain a spreadsheet ledger to document that participants received the gift cards and the cash payment. The spreadsheet will include columns for participant (study) ID#, the item ($25 gift card; $5 cash), the serial # of the gift card, and the date dispensed.

4.7 Risks of Harm/Potential for Benefits to Subjects

A. Description of Risks of Harm to Subjects

- **Reasonably Foreseeable Risks of Harm**

Foreseeable risk of harm, discomfort, hazard or inconvenience	Probability, Magnitude, Duration, Reversal
Fatigue after testing session	Probability: moderate Magnitude: mild to moderate Duration: remainder of test day Reversal: likely resolved by next day
Delayed onset muscle soreness in lower extremities day after testing session	Probability: low Magnitude: mild Duration: 1-2 days after testing session Reversal: likely resolved by day 3 after testing session
Emotional discomfort due to question(s) on questionnaires	Probability: negligible/low Magnitude: mild to moderate Duration: remainder of test day Reversal: likely resolved by next day

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Emotional discomfort during or after meditation	Probability: negligible/low Magnitude: mild to moderate Duration: day of meditation Reversal: likely resolved by next day
Skin irritation under electrode application site after TENS use	Probability: negligible Magnitude: mild Duration: 1-2 days after use Reversal: likely resolved by day 3 after use
Inconvenience associated with finding a drop off location for pre-paid shipping for return of Actigraph device	Probability: low Magnitude: low Duration: same day as drop off day
For those in interventional phase, inconvenience associated with need for participant do use their own mobile phone or device to respond to respond to daily text message re: adherence to treatment	Probability: low Magnitude: mild Duration: throughout the 6-week intervention period for those participating in the interventional phase

- **Risk of Harm from an Intervention on a Subject with an Existing Condition**
  All risks disclosed in the preceding chart are provided with assumption that the participant is HIV+ and may have painful neuropathy in the feet. Risk of fatigue or delayed onset muscle soreness may be greater in individuals who are deconditioned or obese. Risk of emotional discomfort may be greater in individuals with anxiety, depression or past trauma.
- **Other Foreseeable Risks of Harm**
  Other foreseeable risk includes risks a possible loss of confidentiality.
- **Observation and Sensitive Information**
  Not applicable.

B. Procedures which Risk Harm to Embryo, Fetus, and/or Pregnant Subjects
Not applicable.

C. Risks of Harm to Non-Subjects
Not applicable.

D. Assessment of Social Behavior Considerations
Participants whose observed social behavior is indicative of severe psychological distress or violence, participants whose HAD scores are indicative of severe depression or anxiety, and participants whose Pain Catastrophizing Scale score is indicative of clinically relevant catastrophizing will be advised to seek medical attention or counseling. The PI will provide with such participants with a list of mental health recourses and mental health treatment centers in the area where the participant resides.

E. Minimizing Risks of Harm
Procedures to assure confidentiality of data:
All data will ultimately be stored in a password protected folder on the university servers and accessible only to appropriate project team members. Data will be linked only to participant study ID#s, i.e. key codes. The de-identified data file will be shared with Dr. James Parrott (co-investigator and statistician) and other co-investigators as needed for purposes of analysis. A separate secure spreadsheet that links participant ID#s to their names will be kept on a separate password protected folder on a university server available only to Kietrys (PI) and Barberio (co-investigator) and will be accessed only if the code needs to be broken in order to contact a participant based on any measurements or questionnaire responses that suggest need for a referral for medical attention or counseling. Signed consent forms will be scanned into a separate secure password protected folder on the university servers and accessible only to appropriate project team members, after which paper copies will be shredded. Kietrys (PI) is responsible for assuring security of all de-identified data, the spreadsheet that links participant names to

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participant ID#s, and signed consent forms. Any co-investigators and study staff involved with data collection (Ferraro, Lynch, Breen) will be trained by PI (Kietrys) in all security protocols.

Data will be entered into the RedCap platform and RedCap via survey links that are created for this study, and will later transferred to in a password protected folder on the university servers and accessible only to appropriate project team members.
ZENO walkway data will be stored and processed on a password protected laptop dedicated to the ZENO walkway. The laptop with ZENO walkway data will be continuously within the line of sight of Kietrys or Ferraro during data collection and securely stored during transport between data collection locations. ZENO walkway data will be transferred from the dedicated laptop to a secure password protected folder on the university servers. After processing ZENO walkway data with PKMAS gait analysis software, the raw and aggregate ZENO walkway data will be uploaded into the RedCap project.
Mid-thigh pull test data will be uploaded into the RedCap project.
Actigraph data will be transferred from the Actigraph device to a password protected folder on the university servers, after which Actigraph devices will be wiped of participant data and disinfected prior to the device being used by a subsequent participant. After processing Actigraph data with ActiLife software, the raw and aggregate Actigraph data will be uploaded into the RedCap project.
Text messages and responses to text messages about adherence to interventions (TENS and MM groups only during the 6 weeks of home-based treatment) will be done through a study-specific password protected Twilio account, and then uploaded into the RedCap project.

Procedures to monitor subjects for safety and minimize risk of harm during testing:
Study staff will follow CDC and Rutgers COVID precautions (such as wearing a face mask and a face shield) throughout the testing session. Study staff will wash their hands before and after a testing session and sanitize their hands frequently throughout a testing session. All equipment including pens or iPads used for questionnaires will be disinfected both prior to and immediately following a testing session for a given participant. Participants will be scheduled one at a time with no overlap. If more than one participant is scheduled on the same day, there will be a full hour gap between participants to allow time for disinfection of all testing equipment. Participants' appointments will be postponed if they are experiencing symptoms of COVID-19 or are febrile or had a high risk exposure to a COVID infected individual during the week prior to their testing appointment. This will be determined by the PI or study staff calling the participant the day prior to or the morning of their appointment. Prior to testing procedures, participants' resting heart rate, blood pressure, respiratory rate and temperature will be taken. If vital signs values or temperature are outside of acceptable ranges, testing will not proceed on that date. All participants will be required to follow COVID precautions that are in place at the time testing throughout the testing session. Currently, this includes participants wearing masks throughout the session, sanitizing their hands with hand sanitizer prior to the start of testing and prior to leaving the testing session, and maintaining social distance of at least 6' between study team personnel and participants will be maintained except for when testing procedures require closer proximity. All participants will be guided by and supervised by a study team member throughout all testing procedures. During the balance tests that are included the Short Physical Performance Battery, the PI or his designated study team member will stand adjacent to the participant and provide guarding in case the participants experiences a loss of balance. The other test that will require proximity of less than 6' is pain pressure threshold testing. After each test, participants will be asked if they would like to sit and rest before continuing on to the next test. If participants appear to be in any distress or become lightheaded during testing, they will be given the option of lying down on a treatment table or sitting in a chair, and their vital signs will be reassessed.
Procedures to monitor subjects for safety and minimize risk of harm during the period of home-based interventions: Participants in the interventional phase will be notified on baseline testing day that they should contact the PI if any problems arise during the 6 week at-home intervention period. Participants in the TENS will be educated on how to inspect their skin after removing electrodes following a TENS treatment. Because DSP typically causes impaired sensation in the distal extremities TENS electrodes will not be placed on the feet. Rather, the locations will be more proximal at designated points on the lower extremities that have been

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assessed (on the day of baseline testing) by study personnel to have protective sensation as assessed with a 5.07 gauge (10 gram) Semmes-Weinstein monofilament. Participants in the TENS group who do not have protective sensation over the TENS sites in the legs will not be provided with TENS treatment. . In addition, all participants in the interventional phase will be contacted once a week by text message meeting and will be asked if they are experiencing any problems of difficulties.

- **Certificate of Confidentiality**
  Not applicable.
- **Provisions to Protect the Privacy Interests of Subjects**
  The instructions given to participants for all of the questionnaires will include mention that the participant and skip (not respond) to any questions that they don't wish to respond to.

F. Potential Benefits to Subjects

Participants in the interventional phase of the study may benefit as the use of TENS or mindfulness meditation and may experience improvements in a number of outcomes such as pain, quality of life, physical performance and physical activity. Furthermore, participants may become less reliant on pain medication, alcohol or substances for pain relief. The probability of such benefits is expected to be high in those in the TENS and meditation groups, with magnitude ranging from small improvements to large improvements that will vary by individual. The duration of such benefits may be prolonged if the participants continue with the use of TENS or meditation after the study concludes.

5.0 Special Considerations

5.1 Health Insurance Portability and Accountability Act (HIPAA)

We are not requesting a waiver of HIPPA authorization. All data from obtained in the study will be de-identified and linked only to the participant's study ID number, i.e. not health information or data will be linked to their name or other identifying information.

5.2 Family Educational Rights and Privacy Act (FERPA)

Not applicable.

5.3 Code of Federal Regulations Title 45 Part 46 (Vulnerable Populations)

A. Special Populations

- Not applicable.

5.4 General Data Protection Regulation (GDPR)

Not applicable.

5.5 NJ Access to Medical Research Act (Surrogate Consent)

Not applicable.

6.0 Data Management Plan

6.1 Data Analysis

Cross-sectional phase: We will test for baseline differences between those with painful DSP and those without painful DSP for the set of variables using independent t-tests (or Mann-Whitney tests if distributions are non-normal). Differences between those with and without DSP on potential demographic or clinical confounders will be adjusted for statistically.

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Interventional phase: Assuming normality of the outcome variables of interest, between group repeated measures analysis of variance will be used to evaluate differences within and between groups for each outcome separately. In the case of non-normal outcome variable distribution, we will consider transforming the measure to normalize. If normalization is not warranted, then within group changes will be tested using a Friedman's test and between group differences will be compared descriptively. Data will be analyzed using both per-protocol and intention-to-treat analyses in the case of dropouts.

6.2 Data Security

All data will ultimately be stored in a password protected folder on the university servers and accessible only to appropriate project team members. Data will be linked only to participant study ID#s, i.e. key codes. The de-identified data file will be shared with Dr. James Parrott (co-investigator and statistician) and other co-investigators as needed for purposes of analysis. A separate secure spreadsheet that links participant ID#s to their names will be kept on a separate password protected folder on a university server available only to Kietrys (PI) and Barberio (co-investigator) and will be accessed only if the code needs to be broken in order to contact a participant based on any measurements or questionnaire responses that suggest need for a referral for medical attention or counseling. Signed consent forms will be scanned into a separate secure password protected folder on the university servers and accessible only to appropriate project team members, after which paper copies will be shredded. Kietrys (PI) is responsible for assuring security of all de-identified data, the spreadsheet that links participant names to participant ID#s, and signed consent forms. Any co-investigators and study staff involved with data collection (Ferraro, Lynch, Breen) will be trained by PI (Kietrys) in all security protocols.

Data will be entered into the RedCap platform and RedCap via survey links that are created for this study, and will later transferred to in a password protected folder on the university servers and accessible only to appropriate project team members.
ZENO walkway data will be stored and processed on a password protected laptop dedicated to the ZENO walkway. The laptop with ZENO walkway data will be continuously within the line of sight of Kietrys or Ferraro or Lynch during data collection and securely stored during transport between data collection locations. ZENO walkway data will be transferred from the dedicated laptop to a secure password protected folder on the university servers. After processing ZENO walkway data with PKMAS gait analysis software, the raw and aggregate ZENO walkway data will be uploaded into the RedCap project.
Mid-thigh pull test data will be uploaded into the RedCap project.
Actigraph data will be transferred from the Actigraph device to a password protected folder on the university servers, after which Actigraph devices will be wiped of participant data and disinfected prior to the device being used by a subsequent participant. After processing Actigraph data with ActiLife software, the raw and aggregate Actigraph data will be uploaded into the RedCap project.
Text messages and responses to text messages about adherence to interventions (TENS and MM groups only during the 6 weeks of home-based treatment) will be done through a study-specific password protected Twilio account, and then uploaded into the RedCap project.

6.3 Data and Safety Monitoring

A. Data/Safety Monitoring Plan

This study does not pose greater then minimal risk of harm. However, during on-site testing, participants will be closely monitored and supervised to assure safety.
The PI will maintain a record of any concerns or problems reported by participants. If such concerns or problems are serious and/or an adverse event, they will be reported to the IRB.
The PI will review data on an ongoing basis after any baseline (W0) or post-intervention (W7) testing sessions. Participants in the interventional phase will be reminded weekly via text message (using a study specific password protected Twilio account) to contact the PI if they are experiencing any problems or difficulties or have questions. Post-intervention (W7) data will be reviewed by the PI

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(Kietrys) within 24 hours after the collection of data to assess if any data suggests that the participant was harmed.

B. Data/Safety Monitoring Board Details
Not applicable as this study does not pose greater then minimal risk of harm.

6.4 Reporting Results

A. Individual Subjects' Results
Individual results will not be shared with participants. However, if participants have any test scores (such as abnormal vital signs or observed behavior that is suggestive of severe depression or suicidal ideation), they will be alerted of the finding by the PI (Kietrys) and advised to seek medical attention or counseling.

B. Aggregate Results
Study findings will be posted to ClinicalTrials.gov. Participants who wish to review aggregate results of the study will be directly to ClinicalTrials.gov.

C. Professional Reporting
Results of the study will be submitted for presentation in the form of a poster or platform at least one national or international conference such as the American Physical Therapy Association Combined Sections Meeting. It is anticipated that the study will yield at least 2 manuscripts that will be submitted to appropriate peer-reviewed journals such as *Physical Therapy* or *AIDS Care*.

D. Clinical Trials Registration, Results Reporting and Consent Posting
This study includes both an observational phase (cross-sectional phase) and a pilot clinical trial (interventional phase). It will be registered with ClinicalTrials.gov.

6.5 Secondary Use of the Data
Not applicable. Data will not be shared with other researchers.

7.0 Research Repositories – Specimens and/or Data

Not applicable.

8.0 Approvals/Authorizations

Not applicable. Required Departmental Reviews for study personnel from Rutgers have been noted in Section 1.3 of the eIRB application.

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