Study Protocol

ClinicalTrials.gov Identifier: NCT03855111
Official Title: Symptom Management Efficacy Study to Reduce Distal Neuropathy Pain
Abbreviated Title: A Symptom Management Study to Reduce Neuropathic Pain
Other Study ID Numbers: S18-00257
Date: 8-20-2024
NIH NINR Grant No. 1R01NR017917-01
Institution: New York University
PI: Joyce K. Anastasi

Protocol

S18-00257: A Symptom Management Study to Reduce Neuropathic Pain (Acu/Moxa for DSP)

PI: Dr. Joyce K. Anastasi

Purpose of the Study and Background

Purpose of the Study

Peripheral neuropathy is a chronic, debilitating condition affecting quality of life[1-4]. Treatments prescribed to manage distal sensory peripheral neuropathy (DSP)(1) pain, such as nonnarcotic and narcotic analgesics, antidepressants and anticonvulsants, are largely ineffective. This lack of effective treatment and side effects of drug therapy present a challenge to managing painful neuropathy[1, 2, 5, 6]. In HIV, DSP is the most frequent cause of pain[1, 3], affecting 20% - 50%, even when viral load and CD4 levels[6-12] are well controlled. Despite non-use of first-generation antiretroviral agents[3, 9, 13] with recognized neurotoxic side effects(2), the prevalence of DSP among persons living with HIV (PLWH) remains high. *Impact: There are no FDA approved agents to treat DSP pain in HIV[6, 14, 15], and agents tested in randomized clinical trials (RCT) fail to show superiority to placebo[1, 4]. Effective interventions are needed to help PLWH manage DSP pain[16].* This study tests the efficacy of a novel therapeutic approach for chronic DSP pain in PLWH. The literature and our preliminary studies provide a strong rationale for a rigorous, randomized, blinded, sham/placebo and waitlist controlled, parallel groups clinical trial, following CONSORT[17] and STRICTA[18] guidelines(3).

Patient Impact. A critical need exists for effective therapies that reduce DSP pain in HIV. Traditional Chinese Medicine (TCM) is a non-pharmacologic approach to pain management. In the *TCM framework*(4), treatment focuses on correcting the root cause of the DSP to achieve sustained symptom reduction. Real-world TCM practice protocols employ diagnostic assessment of both patient constitution and presenting symptoms to develop an individualized treatment plan. Our preliminary studies show that this individualized (tailored) protocol, and a standard (fixed) protocol, both achieve DSP pain reduction in follow-up at week 15.
Methodology Impact. This application proposes to conduct a randomized controlled clinical trial of two promising non-pharmacologic treatments for HIV-related DSP pain: Individualized TCM treatment (tailored) and Standard TCM treatment (fixed) with comparison to a sham/placebo and WaitList control condition. The testing of both Individualized and Standardized protocols for HIV DSP in the same RCT is novel and will determine their relative merits and inform recommendations for future clinical practice. Additionally, inclusion of both a Sham/Placebo control for secondary effects of Acupuncture/Moxibustion and a WaitList control adds a level of scientific rigor necessary for the inclusion of these findings in future systematic reviews and their value for evidence-based practice.

Specific aims (SA) are:

SA #1: To determine the *efficacy* of Standard Acu/Moxa, Individualized Acu/Moxa, Sham Acu/Placebo Moxa and WaitList to reduce the severity of lower limb DSP pain measured by the *Gracely Pain Scale* at clinically relevant *timepoints*:

- After 6 wks of twice-wkly treatment sessions (the end of the *treatment phase)*
- And at weeks 9, 11 and 15 (the *follow-up phase*)

*Hypothesis for **Specific Aim #1***: There will be at least a 3-level reduction in Gracely Pain Scale (GPS) at the end of treatment; from “moderate” to “very mild”, (Standard > Individualized > Controls); but follow-up benefit will favor Individualized > Standard > Controls.

(1) DSP also known as HIV-Associated Sensory Neuropathy (HIV-SN) refers to neuropathy attributable to HIV itself and/or some HIV treatments. The term ‘DSP’ will be used instead of HIV-SN to refer to this application’s focus on lower extremity pain and associated symptoms.
(2) Antiretroviral agents with associated neurotoxicities eg. “d-drugs” (eg. didanosine, stavudine, zalcitabine)
(3) CONsolidated Standards of Reporting Trials (CONSORT) / STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA)
(4) TCM framework, its fundamental concepts and philosophy, views the patient as a whole[66] and has been integrated throughout this application.

SA #2: To determine *efficacy* of the four conditions to reduce lower limb sensory neuropathy symptoms of DSP (aching/burning, "pins and needles", numbness) measured by the *Subjective Peripheral Neuropathy Screen (SPNS)*, and improve patient-rated measures of effectiveness as measured by the NIH *PROMIS Pain Scale*, the *Clinical Global Improvement* (CGI), *Health-Related Quality of Life (MOS-HIV)* and *Neurological Sensory Testing (NST)*[(5)] at clinically relevant timepoints (stated above).
Hypothesis for ***Specific Aim #2***: At least 30% improvement in NIH PROMIS, SPNS, CGI, MOS-HIV and NST at end of treatment *and* follow-up (Individualized > Standard > Controls); and Sham Acu/Placebo Moxa and WaitList not statistically differ.

SA #3: Compare safety profiles (symptom number/severity/timing) of Standard, Individualized, Sham Acu/Placebo Moxa and WaitList captured by: (a) daily SD, (b) an elicited physical symptom checklist, (c) adverse events from scripted-interviews at each visit, and (d) impairment on neuro/NST.
Hypothesis: ***Specific Aim #3:*** Rates/severities of AEs will not differ between Conditions.

SA#4: To explore which TCM diagnoses, NST findings and pain medication use show the highest separate and combined prediction of patient-rated effectiveness at follow-up.

Background

DSP is one of the most debilitating neurological complications of HIV affecting nearly 1 in 3 PLWH[1, 4, 7-10, 14, 15, 19-21] and reported by 33% of patients within three years of initiating antiretroviral therapy (ART)[7]. Although ART has changed HIV to a chronic condition[9], DSP remains prevalent and under-addressed[14, 22]. Treatment options to manage HIV/DSP pain have limited efficacy[14, 22]. In the United States (US), cost estimates for treating painful DSP exceed $23,000[23] per person/year yet such therapies are often ineffective[1, 22]. A critical need exists for effective interventions to manage painful and debilitating DSP symptoms. Interventions should be effective, acceptable for PLWHs and not produce additional side effects or burden.

DSP and HIV: Post-ART era risk factors for DSP are previous "d-drug" use (i.e. didanosine, stavudine, zalcitabine), advanced age, substance abuse, and increased immune deficiency[9, 21]. Interestingly, the risk for DSP is not associated with ART effectiveness at reducing viral load[9]. Findings from the Central Nervous System Anti-Retroviral Therapy Effects Research (CHARTER) study group suggest that peripheral nerve recovery with ART is incomplete since DSP signs persist after immune recovery and virologic suppression[9]. Currently, the pathogenesis and clinical course of HIV-related DSP remains unclear.

DSP manifests as pain, numbness, tingling in a stocking or glove distribution, and burning over the soles and the distal portion of the toes[22, 24, 25]. Clinical signs of DSP include bilateral ankle reflexes absent or depressed relative to the knee, decreased sensation to vibration, pin prick and temperature with distal sensory loss grading to normal in the proximal limb and generally normal muscle strength[22, 24, 26].

The cornerstone of DSP management is supportive[16]. Cessation or dose reduction is often considered for medications known to be neurotoxic. Medications recognized to cause DSP include dapsone, metronidazole, isoniazid, vincristine, and thalidomide[19, 27]. Toxic medication side effects occur more frequently in people with chronic conditions[28, 29] likely related to the treatment of multi-system problems and multi-drug interactions[28]. To rule-out other etiologies of DSP, clinical assessments considers metabolic disorders (e.g., diabetes, thyroid dysfunction, vitamin B-12 deficiency) and alcohol/recreational drug use[3, 30].

Acupuncture/Moxibustion have been combined in clinical practice for centuries *as a pair*[31]*.* According to Mizutani, the therapeutic effect is boosted when both forms of treatment are used together[31]. Flaws and Sionneau[32] state that peripheral neuropathy is a root deficiency of qi and yin with a branch excess of blood stagnation, dampness and/or damp heat impediment; acupuncture alone *is not* considered the standard of care for this condition[32]. Based on the TCM theory, pathogenesis, diagnoses and treatment principles for the pattern differentiation of DSP, the proposed Acu/Moxa protocol is the optimal method for this syndrome.

[(5)] Neurological assessments with Neuro Sensory Testing (NST) include: muscle strength and reflexes and sensory testing for lower limb vibration, pain and temperature. For this application, this will be referred to as neuro/NST.

A Review of Clinical Acupuncture Studies for the Management of Peripheral Neuropathy

A few published studies and two paper presentations involving acupuncture for DSP in HIV were found. Galatino et al. (N=7)[33], Tosches et al.(N=39)[34] and Goh (N=31)[35], were *non-randomized* studies *without concurrent control*, reported statistical improvement in pain ratings and/or functional status. Galatino used electroacupuncture 20 minutes/day for 30 days; Tosches used twice weekly acupuncture for 6 months and Goh used one to three acupuncture treatments/week for an unspecified length of time. Shlay et al.,[36] conducted a randomized study which used a modified blinded, factorial design of standardized acupuncture, acupuncture control points, amitriptyline and placebo amitriptyline. While statistical improvement was observed at the end of 14-weeks on a global pain relief scale for the acupuncture group this study had considerable flaws including: a change of the randomization scheme during the study; lack of justification for both the acupuncture point selection and control points[36]. Leaders in the research acupuncture field, including Kaptchuk[37] expressed doubt that trial presented credible evidence for the hypothesis. Anastasi et al.'s (N=50)[38] RCT was included in a recent systematic review and meta-analysis of acupuncture for the treatment of neuropathy[39]. This study received high scientific quality ratings and the only study with significant benefit of acupuncture for pain reduction in the primary ITT analysis [redacted]. This study builds on this experience with a larger sample, includes both Individualized and Standard protocols and important controls that will produce an evidence-base critical to moving this science forward.

Research Study Design and Methods

Study Design

196 PLWH experiencing DSP pain are randomized to one of four conditions in a 2:2:1:1 ratio in a prospective, blinded, parallel groups, Sham Acu/Placebo Moxa, WaitList controlled clinical trial. Condition 1, Standard Acu/Moxa (*fixed)*; Condition 2, Individualized Acu/Moxa (*tailored)* based on TCM diagnosis), Condition 3, Sham Acu/ Placebo Moxa (Control) and Condition 4, WaitList (Control). Subjects attend one screening/ intake session, 12 treatment sessions (12 visits for WaitList) and 3 non-treatment follow-ups.

Study Site

The study will be conducted at the NYUCN Division of Special Studies in Symptom Management, Acupuncture Laboratory Suite. [redacted]

Subjects / Anticipated Subject Characteristics. The sample is comprised of adult, PLWH, 18 years and older who function independently and experiencing pain associated with DSP. We anticipate enrolling/consenting 275 and yielding 196 randomized subjects.

Subject Capacity

N/A – All subjects will have the capacity to give informed consent.

Subject / Representative Comprehension

However, we require subjects to be able to read, write and understand English in order to ensure that subjects can complete all questionnaires and daily symptom diaries. After completing the informed consent process the potential subject is asked to restate the overall purpose and main tenants of the protocol. Once it has been determined that the potential subject has an understanding of the study he/she is asked to read through the consent form and ask questions.

[redacted]

Documentation of Consent

After the research staff conducts the informed consent process, the research subject will review all pages of the consent form, then sign and date. The research subject will then receive a copy of the signed consent form for his/her records. The research subject will then initial a form stating they received a copy of the consent form. The original copy of the consent form will be stored in a locked filing cabinet in the research suite.

Costs to Subject

N/A – No Cost to subjects

Compensation

Subject compensation is *pro-rated*. All subjects, (Conditions 1, 2, 3 and 4) will receive $10 for intake/screening session and during the twice-weekly phase. For the follow-up sessions subjects will receive $20, $30 and $40 respectively. All subjects, (Conditions 1, 2, 3, and 4), will receive a total of $220 for attending all study sessions. Additionally, subjects will be given a MetroCard for round trip bus/subway transportation valued at $5.50 or parking fees, at each visit.

Study Schedule

Study Phase	**Screening**	**Treatment Phase** (6 weeks of twice-weekly treatments)												**Follow-up Phase**		
Week Number	1	2		3		4		5		6		7		9	11	15
Session/Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Treatment Number		1	2	3	4	5	6	7	8	9	10	11	12			

Procedures

Subject Recruitment / Screening and Enrollment Procedures / Consent Process

Subjects are recruited using flyers/brochures posted in HIV community-based organizations (CBO), advertisements in newspapers/ magazines with a healthcare section and by informing colleagues (MDs, physician assistants and nurse practitioners) working in the field of HIV in the NYC area. Potential subjects responding to advertisements, flyers or clinician referrals are telephone screened using a scripted guide, to assess for preliminary eligibility. Potential subjects are informed that their participation involve neurological assessments, NST, attending study sessions (1 screening/intake, 12 treatment (or 12 WaitList visits) and 3 follow-up sessions), and completing health related questionnaires. Eligible subjects are mailed an *Authorization to Release HIV/Medical Information* form, for signature, and an information form reflective of the eligibility criteria to be completed by their PCP and returned to the PI for review. Subjects receive pro-rated compensation up to a total of $220 for completing all study visits. Subjects also receive a $5.50 MetroCard per study session to cover round-trip transportation to the study site or parking fees. Other non-pharmacologic, multi-session intervention trials involving similar subject data collection methods (e.g. questionnaire completion, daily diaries) provide higher monetary compensation[40].

Session 1 (Screening/Intake) At the first face-to-face visit, the informed consent process is conducted by the project director (TBN). If the potential subject remains interested in participating after a thorough description of the study, an informed consent form is provided, signed and a copy given to the subject. After the consent process, Dr. Capili, HIV Neuro-NP and nurse scientist, conducts an initial comprehensive standardized neuro evaluation which includes a review of systems, physical exam, and an assessment of motor and NST responses, to assess for evidence of lower limb neuropathy as per inclusion criteria. [Subsequent neuro assessments, at scheduled at time-points, are abbreviated and called, *neuro/NST,* focuses on signs of the lower extremities (muscle strength, reflexes, sensory testing for lower limb vibration, temperature and pain threshold…using Von Frey hairs, Rydel-Seiffer tuning fork etc.]. All assessments are reviewed by the PI, and if additional consultation is required, Dr. [redacted] (Neurology Consultant) will be contacted.

Baseline questionnaires are administered by the project director and a one-week SD is given to the subject to establish baseline symptom severity [eligibility]. Subjects are informed that should the study team identify clinical information from their screening and/or clinical findings requiring clarification and/or treatment by their PCP, their PCP is notified and enrollment may postponed or terminated.

Session 2 (Evaluating subject eligibility/enrollment/randomization/treatment session): Subjects bring in their completed prospective SD to determine enrollment eligibility to the project director. The SD must demonstrate an average rating of "moderate" or greater on the Gracely Pain Scale to be enrolled. Once eligibility is determined, the subject is randomized.

The subject then meets the Diagnostic Acupuncturist (DA) for a TCM Diagnosis and Point Prescription. This is recorded on a prescription card, placed in an opaque envelope and given to the Study Facilitator (SF). The DA is *blinded to all assignments* and ***only*** *diagnose and prescribe points and never treats in this study.* This is to avoid treatment bias. *All subjects* regardless of their assignment is evaluated by the DA, but *only* subjects assigned to the *Individualized* arm (Condition 2) receive the Point Prescription specific to their TCM diagnosis. (see Conditions below)

After the subject is evaluated by the DA, the SF provides the treating acupuncturist (TA) with the appropriate treatment condition/protocol for those randomized to Conditions 1, 2 and 3. The SF introduces the subject to the TA and the treatment session begins. The SF gives the TA the DA point prescription for those randomized to the Individualized arm. To ensure protocol fidelity, the SF monitors all sessions. The SF records and times the sequence of Acu/Moxa protocols, monitors that all points and treatments are administered per protocol, records and maintains case report forms, initiates adverse event forms, assist subjects on and off the treatment table, maintains a safe environment and supplies the treatment room. Condition 4 (WaitList) leaves after reviewing diaries, completing forms, and the DA evaluation.

All treatment sessions are 1 hour in duration. From our Acu/Moxa research experience, the 1 hour time allotment was adequate for the subject to change into a patient gown, receive the intervention and redress. For sessions that require the completion of instruments/questionnaires, an additional 20 minutes is allotted. At the end of each session, subjects receive a new SD.

Follow-up sessions (F/U). Subjects bring in their SD, complete questionnaires/forms, undergo neuro/NST assessment, see the DA for evaluation, receive new SD, schedule next session and receive their compensation fee. No treatments are given at F/U. At the *end of the final F/U* session, the SF unblinds the treatment assignment to the subject. All Control subjects (Sham/Placebo and WaitList) are offered 12 true Acu/Moxa treatments. Post-study subjects are treated away from the study area. A dedicated phone line and voice mail is provided for the SF for these appointments/cancellations. Meticulous efforts are made to preserve blinding as previously employed in our preliminary studies and outlined in our operations manual.

Blinding to Treatment Assignment /Randomization /Concealment: Blinding is achieved by the following. D. McMahon (statistician) prepares the randomization code sequences as “A”, “B”, “C” or “D” (SAS Proc PLAN) in a 2:2:1:1 ratio using the method of randomly permuted blocks[41]. Double-sealed opaque envelopes numbered in enrollment sequence contain three preprinted Avery® labels with the same “A”, “B”, “C” or “D” code: one stays in the envelope, one transferred to the SF’s randomization log and one put in the subject’s randomization case report form. Randomization occurs when subject’s eligibility criteria is verified (session 2). The project director (PD) releases the next envelope in sequence to the SF who uses the code to inform the TA to deliver either Standard Acu/Moxa, Individualized Acu/Moxa, Sham Acu/Placebo Moxa or to WaitList the subject. The key linking the ABCD codes to treatment, known only to the SF, is kept in a double sealed envelope stored in a fire-proof safe at the study site until the final analysis is completed. The first treatment session is initiated immediately following randomization. With the exception of the WaitList group all subjects are blinded to condition assignment. The SF is unblinded to all Conditions. The PD is blinded to Conditions 1, 2, 3 (not WaitList). The following team members are blinded to all treatment and condition assignments: PI, statistician, Neuro-NP, DA, Data Manager, Drs. [redacted].

Conditions: Specific Procedures for *Treatment Conditions*

Condition 1: Fixed	Condition 2: Tailored	Condition 3: Control
Standard Acu/Moxa Protocol	Individualized Acu/Moxa Protocol	Control Sham Acu/Placebo Moxa

All subjects are evaluated by Diagnostic Acupuncturist (DA) to assess for TCM diagnosis and point prescription.

All subjects are *blindfolded* during treatment procedures[6].

All subjects receive Acupuncture/Moxibustion (per condition assignment) by the Treating Acupuncturist (TA).

Only sterile disposable needles (Seirin®, J-type, 30 mm, 38 gauge) are used. Needles are not shared between patients or on different points in the same patient. All procedures are performed according to the guidelines and standards in "Clean Needle Technique for Acupuncturists" published by National Acupuncture Foundation (NAF)[42].

All treatment sessions follow a specific regimen which is point sequenced and time monitored, per protocol condition.

All moxibustion procedures are performed with lighted moxa poles/sticks, made from the dried leaves of *Artemisia Vulgaris* (Mugwort leaf) sold commercially and purchased from one supplier (Pure Moxa Rolls™).

All subjects follow the same study schedule. (Refer to Proposed Protocol Schedule above)

CONDITION 1: STANDARD PROTOCOL (Fixed Acu/Moxa Protocol-oriented Treatment)

Acupuncture: Subjects are to receive point stimulation with needles (termed: "receiving Qi") at classic point locations[43]. *Needling Method* is *reinforcing/ tonification method*, and is performed by inserting the needle at the appropriate depth (per classic text) while the patient inhales. After insertion, the needle is rotated 9 times gently and slowly with small amplitude in a clockwise direction[43].

Rationale. The *acupuncture* component of this treatment is based on classic *TCM theory, the major groupings of TCM diagnoses and imbalance of organ systems for individuals with DSP*. The points are suitable for the treatment of tonifying qi and blood and/or moving qi and blood, and resolving dampness. An expert panel of acupuncturists participated in the selection and review of points, sequencing and timing of this protocol. Based on classic texts, experience of the team, and supportive preliminary studies, this protocol is appropriate and suitable for patients with HIV experiencing DSP.

Moxibustion: Provide point stimulation by Moxa to move and smooth the flow of qi, to provide warmth and nourish the point, channel, and organ system.

Procedure and technique: Indirect moxibustion using lighted Moxa sticks (also called "pole moxa") is used for point stimulation. All procedures are performed according to indirect moxibustion techniques as described in the classic text: Chinese Acupuncture & Moxibustion[43]. Briefly, a burning moxa pole (cigar shaped) is held approximately ***1 inch over the traditional points,*** moved in a clockwise circular motion directly over each point for a period of 2 minutes or until the skin around the area of the point becomes *pink*[43].

Rationale: This moxibustion treatment plan was designed based on TCM theory and practice. It is reported that the stimulation of acupuncture points with moxibustion can provide relief from painful syndromes[31, 44-47]. This protocol is deemed appropriate and suitable for patients with HIV experiencing peripheral neuropathy by our team of acupuncturists, classic TCM texts[31, 43] and our preliminary studies.

CONDITION 1* (STANDARD Fixed Acu/Moxa)	
Acupuncture: SP-10, LV-8, GB-34, ST-36, SP-6, GB-39, KI-3, LI-11	
Moxibustion: BL-17, BL-18, BL-20, KI-1	
*All points are bilateral; the point functions/rationale and specific sequencing and timing of points is located in the APPENDIX	Sources:[31, 32, 43, 48-50]

[6] This procedure has been instituted in all of our acupuncture (including acu/moxa) studies. To date over 6,000 blind-folded protocol sessions have been administered without any issues or complaints about blind-folding. Subjects are explained the blind-folding procedure at the baseline session and prior to the first treatment session.

CONDITION 2: INDIVIDUALIZED (Tailored Acu/Moxa Protocol Treatment) [see attached file for Protocol Specifics]. This condition utilizes TCM diagnostic assessments to provide individualization within the treatment prescription. The Diagnostic Acupuncturist (DA) makes a TCM diagnosis based on their assessment of the subject's unique constitution and symptoms, and formulates a Point Prescription by selecting additional acupuncture points, needling methods and moxibustion points. This individualized protocol is then administered by the Treating Acupuncturist. **Acupuncture**: Subjects receive point stimulation with needles (termed: "receiving Qi") inserted at classic point locations[43]. The individualized protocol consists of Core points which address affected *organ systems* associated with DSP and the additional prescription *points specific to the subject's symptoms* [minimum of two needles, maximum of six needles]. *Needling Method for Individualized Acu/Moxa Protocol* to be prescribed is the *reinforcing/tonification method* (as discussed in Condition 1) or the *reducing method*. The reducing method is performed by inserting the needle at the appropriate depth (per classic text) while the patient exhales. After insertion of the needle, it is rotated 6 times with large and forceful amplitude in a counter-clockwise manner. **Moxibustion**: The procedure and technique are the same as described for Condition 1. However, the DA selects a minimum of three points or a maximum of four points for moxibustion. Rationale: This protocol is *tailored specifically* for the subject's diagnosis according to the unique symptoms being reported at each diagnostic acupuncture (DA) session. The DA selects/*prescribes* points from table below. This protocol was tested and supported in our preliminary studies.

CONDITION 2 (INDIVIDUALIZED Tailored Acu/Moxa)

TCM Diagnosis associated with HIV/DSP	**Core Points for all Individualized subjects**	**Additional Acupuncture Points prescribed by DA for Individualized Subjects corresponding to their specific TCM diagnosis. TCM Diagnostic Acupuncturist selects points from below [minimum of 2, maximum of 6 needles]**
LV Yin Deficiency	Acupuncture; LI 11 (bilateral) ST 36 (bilateral) SP 6 (bilateral) GB 39 (bilateral) Moxibustion; *Will select minimum 3 points or maximum 4 points from points below* BL 17 (bilateral) BL 18 (bilateral) BL 20 (bilateral) KI 1 (bilateral)	KI 2, KI 6, LV 3, LV 13
LV Blood Deficiency		BL 57, GB 37, LV 3, LV 6
LV Qi Stagnation		KI 4, LI 4, LV 3, LV 4, LV 6, GB 35, GB 37, GB 38, GB 40, GB 41, GB 43
SP Qi Deficiency		SP 3, SP 5, LV 13
SP Yang Deficiency		SP 2, SP 5, CV 4
KI Qi Deficiency		KI 4, BL 23, BL 63, CV 4
KI Yin Deficiency		KI 2, KI 6, KI 7, BL 23, CV 4
KI Yang Deficiency		SP 5, KI 7, BL 23, BL 58, CV 4, LI 4
Qi & Blood Deficiency		ST 34, ST 37, ST 39, SP 4, BL 11, BL 63, BL 64, CV 4
Qi & Blood Stagnation		ST 34, ST 37, ST 43, ST 44, SP 4, BL 56, BL 57, BL 63, KI 8, LV 3, GB 31, GB 35, GB 36, GB 37, GB 38
Dampness obstructing channels		ST 32, ST 33, ST 40, ST 41, ST 43, ST 44, SP 2, SP 4, SP 9, BL 59, KI 7, GB 31, GB 37, GB 40, GB 41, GB 43, LV 6

SP=spleen, ST=stomach, KI=kidney, LV=liver, GB=gallbladder, CV=conception vessel, BL=bladder, LI=large intestine (point functions/rationale in APPENDIX) Sources:[31, 32, 43, 48-50]

CONDITION 3: Sham Acu/Placebo Moxa (Control Group). Sham acupuncture: Superficial Needling to Non-points. Subjects receive Sham Acu according to previously established controls[51-53]. The sham points in this study are as anatomically specific and precise as our active treatment protocol so that they are reproducible and consistent. These points are 2-3 cm *away* from the classic /traditional true point location (as listed in Condition 1), not on a meridian, with an insertion depth of 1-2 mm (just sufficient to make the needle stand vertically) and no needle manipulation. *No qi* is elicited. This procedure "minimizes the specific effects of the needling while maintaining its psychological impact" [54](p.200). This method was assessed as credible and

an effective control procedure[52]. While control in acupuncture studies is controversial, Hammerschlag, acupuncture research scholar, reports what is "considered the most appropriate procedure[is] superficial needling at non-points." NIH Consensus Conference/Acupuncture (p. 46)[51]

Placebo Moxibustion: A burning moxa pole (cigar shaped) is held approximately **8 inches above** and 2-3 cm *away* from traditional location (as listed in Condition 1), for a period of 2 minutes. Special and meticulous attention is made on the part of the acupuncturist to **not** generate a heat sensation. The acupuncturist places his/her hand close to the subject's skin to assess for heat sensation intermittently.

In summary, the points, sequence and timing for the Sham Acu/Placebo Moxa are the same as Condition 1, the difference is the location of the points (are non-points), the depth of insertion (1-2mm), the needle technique (no manipulation), *no qi* elicited and moxa technique (8 inches above and away from point).

Sham needling is controversial. However, we have employed all of the recommendations that minimize the physiological effects and maintain the psychological impact[53]: (a) as stated above, needles are inserted superficially; (b) non-points are instituted; and (c) no manipulation of the needle. Also, we have tested *this sham needling and placebo moxa* procedure in our prior Acu/Moxa R01 studies. (see footnote[55])[(7)]

CONDITION 4: WaitList (Control Group)

Subjects randomized to the WaitList condition experience all aspects of study participation with the exception of exposure to acupuncture and moxibustion (during the study). They undergo all screening and eligibility assessments; attend twice weekly visits for six weeks; attend all scheduled follow-ups; submit and review their symptom diaries, update concomitant medication, adverse event data, complete assessment instruments; be examined by the Diagnostic Acupuncturist and receive neuro/NST assessments. In all respects, participants in the WaitList group receive the same concern as subjects assigned to the other groups. Other HIV studies with WaitLists have successfully maintained subjects in study from 4 to 6 months[56, 57]. Similar to our proposal, those studies also provided the study intervention after the final follow-up session[57].

Outcome Measures [redacted]
Symptom Diary (SD) provides a *daily* multi-dimensional picture of Distal Sensory Peripheral neuropathy (DSP): *Gracely Pain Scal*e, *Subjective Peripheral Neuropathy Screen (SPNS)*, and a *dermatome chart* to record localized report of sensations. The GPS is a Likert magnitude-estimation log-scale of sensory pain[58-60]. Subjects rate their DSP pain by selecting one of 13 words to describe their average and worst DSP pain "Nothing"=0 to "Extremely intense"=12. As per instrument instructions, weekly averages of log scores are analyzed. The Gracely pain score, as a primary outcome in most neuropathy pain studies among HIV/AIDS patients[58, 60-63], demonstrates strong reliability and validity[64]:between-group (r = 0.97), within sessions (r = 0.99) or between experiments (r = 0.99). SPNS has been used to evaluate AIDS patients for sensory neuropathy by NIH/NIAID AIDS Clinical Trials Group[59]. Subjects describe type (aching/burning, "pins and needles", numbness), location (hands/arms, feet/legs), and severity of symptoms. Two sub-scores are computed: Average Severity Score is the mean severity score; the clinical severity grade indexes the highest symptom severity score of any symptom. The SPNS is a valid tool to observe (track/monitor) neuropathic symptoms, evidenced by highly significant Spearman's correlations between the neurological exam severity grade and the Average Severity Score (r_s = 0.65), and the Clinical Severity Grade (r_s = 0.65)[59]. The construct validity, has been assessed by comparing the results between HIV-positive patients diagnosed with or without neuropathy[59]. The reliability of the SPNS, Cronbach's alpha yielded 0.86 for the six symptoms (3 types x 2 locations). An image depicting five dermatomes (both front and back lower extremities) is used to record the intensity, type and duration of DSP sensation at enrollment, the end of the treatment phase and the end of follow-up. This dermatome-based diagram is devised to track the DSP symptom identified as the participant's primary complaint. Self-report is considered the most reliable indicator of the existence and intensity of pain [65]. Additional Information Recorded in Symptom Diary: *Medication Record*. All medication dates taken, name(s),

[(7)] We have chosen not to use the Streitberger placebo needle (Kaptchuk, 1998). The placebo needle has a blunt tip, secured to a hollow handle, allowing needle to retract when applied to skin. To use placebo needle, a plastic ring with an adhesive is applied to skin. Needle is then inserted, creating a pricking sensation, simulating skin penetration. The same procedure must be conducted for true treatments, replacing placebo needle with real needle in order to penetrate the skin. Although novel, several problems are noted: (1) body hair makes application of adhesive difficult and painful on removal, (2) placebo needle will not work on all points e.g. feet, toes, or body areas like KI 3, and (3) device may not allow for various needling methods.

dose, frequency and time taken are recorded. In addition, there are a few short questions asking about daily HIV medication. "Did you take all of your HIV meds today at each of the time points?" If there is a change in medications, subjects record those changes and inform study staff. There are ten general well-being questions, and if applicable, menses onset.

Clinical Global Impression Scale (CGI). This scale measures *severity of illness* and *global improvement*. They are Likert scales, with seven descriptors. The severity of illness scale measures global severity of symptoms [in the context of peripheral neuropathy]. The patient rates discomfort from peripheral neuropathy on a scale of 0= No discomfort to 6= Very severe discomfort. The global improvement scale measures the level of change from initial severity: 0= No improvement at all to 6= Great improvement[66, 67]. CGI is usually administered at several intervals: pre-intervention, during, and post-intervention. The CGI is recognized as a "well known, cross-culturally valid measure" with test-retest reliability > 0.70 and suitable convergent, discriminant and criterion validity; and ROC AUC $\pm$ SE against gold-standard assessments of global improvement of 0.84 $\pm$ 0.06 (95% CI 0.72 – 0.97)[68].

PROMIS Pain Questions. The NIH Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Intensity short form is recommended to assess "how much a person hurts" based on the evidence that pain intensity is a "fairly homogeneous dimension" and that this instrument is universal rather than disease-specific. Three Likert-scaled items ask, in the last 7 days, the worst pain intensity, the average pain intensity and the intensity of the pain right now: all scored from none (=1) to very severe (=5) with a conversion to a T-score with median of 52.1 and SE = 2.96. The pain intensity scale has moderate correlation with the Spine Oncology Study Group Outcome Questionnaire (SOSG-OQ) pain scale, 0.65; but good factor loading with the underlying trait for pain, 0.75; and showed high reliability over a wide range of patient abilities, 0.91[69].

Neurological Evaluation – Neuro Assessment with Neuro Sensory Testing Forms. The initial comprehensive standard neuro evaluation form is comprised of a review of systems, physical exam and an assessment of motor and neuro sensory testing (NST) responses. The initial evaluation is conducted to rule out neurological conditions responsible for DSP and to record clinical findings. Subsequent neuro assessments with NST are abbreviated evaluations, focusing on lower limb assessments (muscle strength, reflexes, sensory testing for lower limb vibration, temperature and pain threshold…using Von Frey hairs, Rydel-Seiffer tuning fork etc.). The neuro/NST also serves to monitor for clinical safety and findings[26].

MOS-HIV. Consists of 35 health-related quality of life questions in HIV that assesses ten dimensions of health (overall health, pain, physical functioning, role and social functioning, mental health, energy/fatigue, cognitive function, health distress and QOL)[70]. Internal consistency reliability of physical health and mental health summary scores range from 0.90 to 0.92 and 0.91 to 0.94 across different samples, respectively[70, 71].

Descriptive Measures

General Health History Form Includes general health history, medical conditions, procedures, interventions, current review of symptoms, medication(s), over-the-counter medications and supplements.

Symptom Checklist. A brief assessment of sentinel symptoms associated with HIV disease progression and side effects of acupuncture treatment. New and changing symptoms will be attributed to the respective treatment condition. Symptoms rated as severe will be recorded and tracked as adverse events[72, 73].

Diagnostic Acupuncturist Assessment Forms (Initial evaluation form and Brief version). The DA records information obtained from the *initial* pre-treatment evaluation and at scheduled sessions (brief version). DA assessment consists of a review of systems, questions about pain, quality of pain, discomfort, and other related symptoms that assist in making a diagnosis (i.e., headaches, sweating, thirst, menses, appetite, urination, bowel movement, energy level, sleep, appetite, digestion, and emotions). Tongue/pulse assessments also recorded. DA evaluations are scheduled once a week, immediately prior to treatment sessions. For twice-weekly sessions, the DA's 1st TCM diagnosis and point prescription of the week are carried forward to the 2nd session of that week. DA also assess at follow-up sessions.

Treating Acupunturist Form. Tongue and pulse assessments are recorded by the TA at every treatment session. The TA is ***not*** permitted to ask diagnostic questions or inquire about the severity of symptoms. Dialogue is professional and kept to a minimum with subjects.

Credibility Assessment. This 6-question, patient-rated instrument was adapted from an acupuncture credibility assessment scale[74]; "6-point" scale, from 1= very confident to 6= not at all confident. Items include: (Q1.) Logic of Acu/Moxa treatment; (Q2.) Confident that the Acu/Moxa treatment you received is true [blinding]; (Q3.) Confident that Acu/Moxa treatment will be successful [expectation]; (Q4.) Confident in recommending to a friend; (Q5.) Confident that peripheral neuropathy symptoms improved with study treatments; (Q6) Likelihood of this treatment in decreasing symptoms in other conditions.[for Conditions 1, 2 & 3]

Mini-Mental State Instrument[75]. A short mental status assessment is essential since the intervention requires frequent sessions and instruction, the completion of measures, and subject's full attention and memory recall.

Other Measures. Demographic Information Questionnaire: assesses social factors suggested by the public health epidemiology literature as influencing health promotion behaviors. The questionnaire includes age, educational background, occupation, adults and children who live with the subjects.

Tongue Photographs. Tongue photographs will be taken to provide objective evidence of tongue observations/assessments. In TCM, the tongue provides a geographic map of the organ systems and may be useful in identifying morphologic patterns associated with this condition.

Note: Tongue photographs are optional. If currently enrolled subjects are interested in participating in the tongue photograph, they will be re-consented.

A number will be assigned to the image. No names will not appear on the photograph or file label.

Characteristics of the Research Population

Number of Subjects

The total number of subjects expected to enroll/consent is 275. This was adjusted to account for screened failures. Our sample size remains at 196 over five years [redacted] Sample size determination (see below)

Identification and Inclusion of Subjects

Subjects will be recruited by the PI and Co-investigators by informing Infectious Disease, HIV and Neurology practitioners, internists, family practitioners, and nurse practitioners in the New York City area about the study. Advertisements will also be published in select New York newspapers/ magazines which have healthcare sections. Additionally, public service announcements, posting in the Clinical Trial Registry and the HIV/AIDS group websites will be implemented. Potential subjects responding to ads or practitioner referrals will be telephone screened by the research staff to assess study eligibility. Potential subjects, screened and meeting eligibility criteria, will be told that the PI/ research staff will need to contact their provider (pending receipt of medical information release) to verify their (potential subject's) diagnoses and suitability for study. Written documentation from their medical provider will be required. Potential subjects with a diagnosis of HIV DSP confirmed by their medical provider will be scheduled for an intake session where they will be given more information about the study. If they are interested and meet eligibility/inclusion criteria, a more detailed description of the project and the informed consent process, including written consent from the subject, will be completed. Informed consent will be administered by the project research staff trained by the PI. All subjects will receive a copy of the consent form.

Targeted/Planned Distribution of Subjects by Sex/Gender and Racial Ethnic Group:

This study will enroll *men* and *women, 18 years of age or older*, HIV+ or AIDS diagnosed, with a history of DSP of the lower extremities for three months or greater and experiencing "moderate" pain.

Gender and race/ethnicity enrollment estimates are based on HIV/AIDS New York City statistics (www.nyc.gov/html/doh/html/ah/hivtables.shtml), therefore, a larger proportion of the subjects will be men and will self-report as black or Hispanic.

Description of Subject Selection Criteria and Rationale for Selection of Sex/Gender and Racial/Ethnic Group:

Our estimate of sex/gender and racial/ethnic group enrollment is also based on the NYC HIV/AIDS statistics. Subjects will be enrolled, if they meet all study eligibility criteria.

Rationale for Exclusion of Sex/Gender and Racial/Ethnic Group:

No individual from any racial/ethnic groups will be excluded if they meet eligibility criteria and are willing to participate in this study.

Description of Proposed Outreach for Recruiting Sex/Gender or Racial/Ethnic Group:

To ensure that we are congruent with NIH guidelines for *minority recruitment* we have reviewed the NIH's Outreach Notebook and the NIH Clinical website and incorporated many aspects of their initiatives into our plan. *Advertisements* will be published in select New York newspapers which have healthcare sections reaching diverse populations in our NYC metropolis. We will be in contact with the University's public relations department to assist us with *Public Service Announcements*. We will post the study in the *Clinical Trial Registry, ClinicalTrials.gov and the HIV/AIDS support group websites*. Our minority recruitment plan will also consist of community outreach presentations in ethnically diverse community forums such as public libraries and religious organizations. NYC is one of the most racially and ethnically diverse cities in the US. Our study site is located in Lower Manhattan (NYC) which is rich in ethnic and racial diversity. Study flyers and brochures will be sent to community agencies, hospital clinics and local health fairs. We also have strong collaborations with clinicians from New York State AIDS Designated Clinical Centers located in NYC. We have used these recruitment methods successfully in recently completed HIV studies and have had greater than 75% of the sample composed of blacks and Hispanics and approximately 22% to 38% women.

Description of subjects and subject enrollment *estimates based on National, State and Local statistics.*

Gender & Racial/Ethnic Composition of Adults/Adolescent *living* with HIV/AIDS in the United States and New York state

		Number of persons living with HIV/AIDS January 2017, New York State (NYSDH)**	Number of persons living with HIV/AIDS, January 2017 New York City (NYCDOH)***	***Study Estimates*** Gender/Minority Inclusion
Gender	Female	32,444 (29.0%)	25,026 (28.5%)	56
	Male	79,489 (71.0%)	62,643 (71.5%)	140
	Total	111,933	87,669	**196**
Race/Ethnicity	White, not Hispanic	22,824 (20.4%)	14,843 (16.9%)	33
	Black, not Hispanic	45,769 (40.9%)	38,348 (43.7%)	86
	Hispanic	35,849 (32.0%)	29,916 (34.1%)	67
	Asian/Pacific Islander	1,677 (1.5%)	1,501 (1.7%)	2
	American Indian/Alaska Native	65 (0.1%)	56 (0.1%)	1
	Other	5749 (5.0%)	3,005 (3.5%)	1
	Total	111,933	87,669	**196**

**www.health.state.ny.us/diseases/aids/statistics/

***www.nyc.gov/html/doh/html/ah/hivtables.shtml

Note: This table this is based on NY State and NYC data on HIV/AIDS. The Race/Ethnicity categories from these agencies differ slightly from the NIH Targeted/Planned Enrollment Table categories.

Inclusion/Exclusion Criteria

Inclusion Criteria
☐Men and women, 18 years of age or older, HIV+ or AIDS diagnosed, with a *history* of DSP of the lower extremities for the past *three months or greater.*
☐Primary care provider (PCP) verification of HIV status, diagnosis of DSP, & subject clinical suitability for the study.(8)
☐Evidence of lower limb neuropathy (bilateral ankle reflexes absent or depressed relative to the knee, decreased sensation to vibration, pin prick and temperature with distal sensory loss grading to normal in the proximal limb)[58]
☐GPS rated pain severity of "moderate" or above, documented in 1-week prospective self-report symptom diary (SD).
☐Any antiretroviral(1) Rx must have 3 months of stable regimen (same drugs, dose & frequency) prior to enrollment.
☐Any pain medications must have 3 months of stable regimen prior to enrollment (2).
☐Those on a stable pharmacologic regimen are expected to remain on the regimen for the duration of the study.
☐Must understand and agree to complete daily symptom diaries for the duration of the study.
☐Successfully complete a mini-mental status exam[75] (obtaining a score of 24 or above).
☐Ability to read and write English, in order to complete questionnaires and subject diaries.

Exclusion Criteria
☐Any acute condition requiring medical care (eg. opportunistic infection).
☐Conditions that may mimic HIV DSP symptoms: i.e. diabetes(3), coagulopathies, B12 deficiency, etc.
☐Use any topically applied medications to the lower extremities.
☐Alcohol and/or substance dependence.
☐Use of injectable corticosteroids *or* any medications known to be neurotoxic within 3 months prior to enrollment.
☐Pregnant women or unwilling to use an acceptable form of birth control(4).
☐Receiving acupuncture within 6 months prior to enrollment.

Exclusion Criteria continued

☐Any history of receiving moxibustion [rationale: subject may recall heat sensation].
☐Currently receiving any other complementary therapies such as herbs, massage, reiki etc.
☐Relocation or plans that interfere with attending all of the planned study sessions and/or recording SD information.

(8) The statement of suitability is specific to our IRB requirements, that all investigators contact the patient's medical provider to ascertain that there is agreement that their patient is clinically suitable for any/all clinical studies in which they are planning to enroll. To date, providers have been supportive and agreed that their patients were suitable. This provision also presents a means to establish communication with providers.

(1) *Antiretrovirals*. To minimize the chance that changes in symptom severity may be attributable to new antiretroviral therapy side effects, we require that all patients on an antiretroviral combination therapy complete their initial 3 months prior to enrollment in this study. Any ART medication changes are examined as a time-dependent covariate.

(2) *Medications*. Subjects are asked to inform the study staff prior to changing their *pain and/or other medications* to assure all medication changes are recorded. Subjects who start, stop or change dosage of any ongoing medications are asked to record the name, dosage and frequency in the medication record (located in the SD). Subjects meeting inclusion/exclusion criteria who are taking medication for DSP pain are allowed to continue on a stable regime. A criterion that totally denies the use of medications to reduce symptoms would be unethical and unrealistic, as well as potentially resulting in non-adherence to the study protocol (missing sessions and/or not being truthful in their medication record contained in the symptom diary). Therefore, subjects are asked to consult with the investigator or study staff if they anticipate or decide to change any of their medications so we can record all changes if they occur. Medication procedures similar to this procedure have been instituted in many symptom management studies examining treatment efficacy in clinical trials. Medication exposure are examined as a time-dependent covariate.

(3) *Diabetes*. Diabetes peripheral neuropathies have etiology, natural history and clinical course different from that of HIV and is not within the scope of this project.

(4) *Pregnancy*. All women are required to take a beta urine HCG test (pregnancy test kit) to rule out pregnancy. Must be willing to use an acceptable form of birth control.

Sample Size Determination Calculation

For power and sample size calculations, our pilot data indicated that, at final follow-up, the improvement in weekly average GPS (log scores) was IND > STD > Control. For IND, the average within-subject improvement was -0.74 ± 0.63 from baseline of 1.25 ± 0.38; for STD was -0.33 ± 1.03 from baseline of 1.21 ± 0.20; for Control was -0.19 ± 0.98 from baseline of 1.30 ± 0.22. These are clinically meaningful reductions in GPS-rated pain (between 30% -- 50%). We calculated sample size for two separate tests (80% power + 5% alpha) using one-way analysis of covariance with the baseline value of GPS as a continuous covariate: a) H_1 either Standard, Individualized or both are superior to control; b) H_1 Standard and Individualized are different from each other. Effect sizes assume the two active treatments are 0.54-SD and 1.08-SD superior to control: calculations (SAS PSS 3.1) indicate 55 analyzable subjects are required for two active and the pooled control groups (sham/placebo and WaitList). In secondary analyses will assess the Controls separately. The linear mixed models for repeated measures (LMMrm) approach proposed for the statistical analysis is more efficient than the one-way ANOVA method used for sample size calculations here and is capable of estimating both the within-group differences at different times and the between-group differences at different time points. The calculated n=55/g will be inflated by 19% for attrition (N=196) and randomized 2:2:1:1 to the 4 conditions.

[redacted]

Data distributions will be examined and transformed, if necessary. Baseline differences among groups will be compared with one-way ANOVA or Chi-Square analysis, as appropriate, and covariates with p-values < 0.10 will be assessed in efficacy models as potential confounders. Missing data mechanisms will be assessed prior to analysis and adjustment or blocking incorporated as appropriate. Between-group differences in repeatedly measured outcomes (SA#1& #2) will be evaluated under intent-to-treat with LMMrm with fixed effects (Diagnostic DA, treatment group and time); random effects (subject and intercept) and a covariance matrix for within-subject autocorrelation chosen by empirical modeling prior to inferential testing. We will test a separate model for each outcome without adjustment for multiplicity. Primary analyses will pool controls[41] to assess overall treatment affects, whereas secondary analyses will assess control group differences on efficacy estimates with apriori defined analyses[76]. We will also assess baseline covariates, expectation of benefit (Credibility instrument Q3) and success of blinding (Credibility instrument Q2) on outcome in secondary models. We will evaluate safety data (SA#3) with non-parametric statistics for rates, proportions and time to events. For SA#4, we will estimate the cross-sectional and longitudinal association between TCM diagnoses, neuro/NST assessment and pain medications with change in symptom severity using multiple correlation/regression analysis.

Vulnerable Subjects

N/A

Data Monitoring

Data Safety Monitoring Report: A data safety monitoring report is submitted annually to the IRB.

Institutional Review Board

The protocol will undergo full IRB review prior to the initiation of the study and annual renewal per NYU IRB policy. All serious adverse events is reported to the IRB per institution policy.

Quality Assurance Plan: Patient safety is monitored by review of subject completed physical symptom checklists at each visit and structured elicitation of the occurrence of adverse events. All adverse events are reviewed by the PI for clinical evaluation and action. All adverse events are detailed and summarized for the IRB for review.

Ongoing Internal Monitoring of Data: In addition to D. McMahon's statistical role in this project, he will establish data quality control mechanisms, data archiving and data security procedures according to industry standards. The results of quality control audits are used to assess project implementation and maintain data quality. Data quality control is accomplished by 100% validation of source documents to case report forms (CRF) and case report forms to database values. The data manager meets regularly with Mr. McMahon.

For all measures, CRFs are created with standard headers for tracking study ID, date, study visit, and staff member responsible for data collection. Acceptable values are listed on the CRF. Explicit procedural instructions and item definitions appears on each CRF. Additional protocol management CRFs are created on which to record the administrative events of a subject's participation in the study: i.e., initial recruitment, assessment of inclusion/exclusion criteria, subject enrollment, attendance at scheduled visits, termination from the study and unscheduled visit contacts. Safety related CRFs are created and used to record adverse events. Concomitant medications are recorded in the daily symptom diary.

Internal monitoring include data quality mechanisms, security procedures, data screens, recruitment, screening; Case report forms, QA monitoring, safety, adverse events; tracking enrollment, attendance, missed sessions; staff training records, Paper records: appropriately stored, study logs; Regulatory – Annual IRB approval; Study staff Citi Training documents, Professional staff Licenses on file; Study staff team meeting record/binder.

Data Monitoring / Quality Assurance

Missing Data/Attrition/ Mid-study Health Events, Suspension of Treatment, Participant Drop-outs

Missing Data Under the *intent-to-treat principle*, the data from all randomized subjects who receive one or more treatments are included in the model. For efficacy analyses, we evaluate the missing-data mechanism as proposed by Heitjan[77]. If missing data cannot be classified as missing-completely-at-random, we will employ maximum likelihood analysis available for random effects models in SAS Proc MIXED[78]. Missing data are not imputed.

Attrition Inevitably some subjects will miss or cancel sessions. The 'visit window' for determination of missed visits for the twice-weekly treatment phase and the non-treatment follow-up phase is plus or minus 3 calendar days and 7 calendar days, respectively. Failure to attend a visit within the 'visit window' will count as a missed visit. A visit attended outside the 'visit window' is considered an unscheduled visit. The schedule of scheduled visits is unaffected by the pattern of missed visits. Subjects missing three or more sessions may be dropped from the study for non-adherence at the discretion of the PI. Dropped or attrited subjects are not replaced by new enrollees. An attrition factor was incorporated in our sample size determination to accommodate for potential dropouts and lost subjects. Multi-session treatment studies may present challenges to data completeness and retention. We are adopting the following rules: A subject missing up to three consecutive treatment sessions may be withdrawn at the discretion of the PI. We believe longer lapses can jeopardize the study integrity. Subjects dropped from the study and subjects who withdraw or fail to return to complete the

protocol will contribute data up to the point of dropout/withdraw or termination.

Data Storage and Confidentiality

Confidentiality. No names or identifying information will be included in research reports. Subjects' personal identifying information does not appear on questionnaires. Subjects will be given unique code numbers and information about them will be organized by this anonymous code number, not names. The list of code numbers and names will be kept in separate locked cabinets accessible only to authorized research staff. All computers are encrypted and have passwords and timed screen savers requiring password.

Risks

There are minimal physical and psychological risks to subjects in the *Standard, Individualized and Sham Acu/Placebo Moxa control conditions*. All needling and moxa will be performed by experienced and licensed acupuncturists trained in TCM. Acupuncture injuries reported in the literature have largely been due to "mishandling of the needles" (National Academy of Acupuncture & Oriental Med., 5/95). The most serious injuries which have been reported from mishandling are: organ puncture, infectious disease transmission (hepatitis), contact dermatitis and spinal cord injury (mostly outside US). The needles used in this study will be sterile, stainless steel, one-time use, and packaged in individual blister packs. The risk associated with moxibustion is that, if ash from the moxa flicks on to the subject's skin, the heat from the ash can result in a blister which could scar. Moxa is never performed on the face. Pole/Stick moxa will be used. All subjects will be observed closely for the duration of each session. If a subject is uncomfortable with the treatment he/she can terminate *at any time*. For the Sham/Placebo and WaitList subjects, true Acu/Moxa treatments will be offered to them at the end of their last follow-up session.

There are minimal physical and psychological risks to subjects in the *WaitList condition*. The *WaitList* attend all study visits, complete questionnaires, fill-in daily symptom diaries, and undergo a neuro evaluation, neuro/NSTs and TCM assessments exactly as implemented for subjects in the other three conditions. Subjects continue under the usual care of their primary providers.

The PI and her team have been conducting acupuncture clinical trials for several years. To date, over 8,000 protocol sessions have been administered without any incidents and/or serious adverse events.

Subjects will be told that this study will address level of functioning and symptoms. Therefore, subjects can expect and prepare for questions addressing daily activities and chronic, distressing symptoms. This minimizes the chance that subjects will be upset by the questionnaires.

Subjects who receive treatment at NYU Medical Center (NYUMC) will be told their agreement or disagreement to participate will not affect the services they receive from NYUMC.

Procedures for protecting against or minimizing potential risks

Adverse Events and/or Clinical situations. In the event a pathological sign or symptom (physical and/or psychological) is reported by the subject to a research team member, observed by one of our staff, or based on questionnaire/symptom checklist/symptom diary response, the subject will be referred to the PI immediately for evaluation. The PI will review documentation, meet with the subject and determine the appropriate action. The PI will consult with Drs. Capili and Marder regarding clinical situations should they arise. If an urgent clinical situation arises, the staff will access the emergency room at NYU and/or Bellevue Medical Center (one block from the study site). Study staff will complete adverse event forms and report to the IRB and NIH program officer for review. Based on our preliminary studies and other acupuncture studies (including moxa), no clinical situations required urgent care. The same procedures have been followed without incident in our previous studies.)

Potential Benefits of the Proposed Research to Subjects and Others

Subjects may or may not receive a direct benefit from exposure to the treatments studied in this project. However, the subjects, the lay public, and the scientific community may learn more about a TCM approach for managing the symptoms of HIV/DSP. In this study, all subjects will have access to an active treatment, including those in the Sham Acu/Placebo Moxa Control and the WaitList Control post-study. Subjects will receive compensation for their participation and travel. In addition, should any physical or mental health problems arise with subjects during this study, appropriate referrals will be made. Subjects may also contribute to the advancement of acupuncture science through their participation in this study and will provide scientists and clinicians with additional evidence to evaluate the efficacy of Acu/Moxa for the management of DSP symptoms. The risks of this research are small, whereas the potential benefits may transcend the subjects to the HIV community at large. This is a rigorously designed RCT incorporating STRICTA and CONSORT guidelines to ensure that the findings from this study can be communicated and replicated across disciplines and settings (i.e. clinical or research).

Payment for Participation / Compensation

Subject compensation is *pro-rated*. All subjects, (Conditions 1, 2, 3 and 4) will receive $10 for intake/screening session and during the twice-weekly phase. For the follow-up sessions subjects will receive $20, $30 and $40 respectively. All subjects, (Conditions 1, 2, 3, and 4), will receive a total of $220 for attending all study sessions. Additionally, subjects will be given a MetroCard for round trip bus/subway transportation valued at $5.50 or parking fees, at each visit. Although this compensation is modest, it is deemed to be appropriate and supported by the information obtained from our earlier work. Subject compensation for this study is pro-rated and is not only for attending sessions but for completing research instruments and daily symptom diaries. Literature suggests that *pro-rating* compensation across multiple visits reduces the possibility of inappropriately influencing someone to stay in a study just to receive a lump sum payment[79]. Escalating incentives are often used in longitudinal studies and/or studies with multiple follow-ups, where certain data points are important[80].

Data and Safety Monitoring Plan

Provisions for monitoring data collected to ensure the safety of subjects.

DSMP initiator: PI.

Data Safety Monitoring Report: A data safety monitoring report is submitted annually to the IRB.

Institutional Review Board
The protocol will undergo full IRB review prior to the initiation of the study and annual renewal per NYU IRB policy. All serious adverse events is reported to the IRB.

Quality Assurance Plan: Patient safety is monitored by review of subject completed physical symptom checklists at each visit and structured elicitation of the occurrence of adverse events. All adverse events are reviewed by the PI for clinical evaluation and action. All adverse events are detailed and summarized for the IRB for review.

Ongoing Internal Monitoring of Data: In addition to D. McMahon's statistical role in this project, he will establish data quality control mechanisms, data archiving and data security procedures according to industry standards. The results of quality control audits are used to assess project implementation and maintain data quality. Data quality control is accomplished by 100% validation of source documents to case report forms (CRF) and case report forms to database values. The data manager meets regularly with Mr. McMahon.

For all measures, CRFs are created with standard headers for tracking study ID, date, study visit, and staff member responsible for data collection. Acceptable values are listed on the CRF. Explicit procedural instructions and item definitions appears on each CRF. Additional protocol management CRFs are created on which to record the administrative events of a subject's participation in the study: i.e., initial recruitment, assessment of inclusion/exclusion criteria, subject enrollment, attendance at scheduled visits, termination from the study and unscheduled visit contacts. Safety related CRFs are created and used to record adverse events. Concomitant medications are recorded in the daily symptom diary.

Data Monitoring / Quality Assurance

Missing Data/Attrition/ Mid-study Health Events, Suspension of Treatment, Participant Drop-outs

Missing Data Under the *intent-to-treat principle*, the data from all randomized subjects who receive one or more treatments are included in the model. For efficacy analyses, we evaluate the missing-data mechanism as proposed by Heitjan[77]. If missing data cannot be classified as missing-completely-at-random, we will employ maximum likelihood analysis available for random effects models in SAS Proc MIXED[78]. Missing data are not imputed.

Attrition. Inevitably some subjects will miss or cancel sessions. The 'visit window' for determination of missed visits for the twice-weekly treatment phase and the non-treatment follow-up phase is plus or minus 3 calendar days and 7 calendar days, respectively. Failure to attend a visit within the 'visit window' will count as a missed visit. A visit attended outside the 'visit window' is considered an unscheduled visit. The schedule of scheduled visits is unaffected by the pattern of missed visits. Subjects missing three or more sessions may be dropped from the study for non-adherence at the discretion of the PI. Dropped or attrited subjects are not replaced by new enrollees. An attrition factor was incorporated in our sample size determination to accommodate for potential dropouts and lost subjects. Multi-session treatment studies may present challenges to data completeness and retention. We are adopting the following rules: A subject missing up to three consecutive treatment sessions may be withdrawn at the discretion of the PI. We believe longer lapses can jeopardize the study integrity. Subjects dropped from the study and subjects who withdraw or fail to return to complete the protocol will contribute data up to the point of dropout/withdraw or termination.

External Monitoring - TBN

An external, independent monitor, not associated with this study or the Division of Special Studies in Symptom Management, will conduct annual monitoring. The goals of the monitoring are to: assess for fidelity of allocation concealment, review the randomization/blinding procedures, documentation of staff training for Acu/Moxa study protocol, subject accrual data and study logs, documentation of the administration of treatment protocols including treatment logs, symptom checklists, assess confidentiality and data security, assess for subject safety: review records for adverse events and serious adverse events, review regulatory compliance records: IRB protocol, consent forms, CRFs, review data entry manual and evaluate process for accurate data entry, prepare a written summary of findings.

External Monitor: (TBN) (Credentials – Clinical Trial Experience, graduate degree, experience in scientific review and industry standards). Main areas for the review and report include: Accrual, Treatment Protocol documentation, Accuracy of Data, Confidentiality and Security of Data, Subject Safety, Regulatory Compliance, Conclusion.

Medical Oversight

Dr. [redacted] will have regular contact with the PI and staff on study progress. She will review protocol manuals, maintain weekly contact with the PI to review new subject/candidates for enrollment, progress and any clinical issue(s) and/or adverse events that may arise. She will provide ongoing collaboration for the duration of the study. Dr. Capili is on-site and will conduct neuro/NST assessments during the course of this study to monitor for subclinical neurological findings and/or clinical conditions which may require further evaluation or referrals. Should impairment worsen from initial assessment, Dr. Capili will review previous assessments, interview the subject focusing on potential causes of increased impairment, conduct a targeted clinical assessment, notify PI and Dr. [redacted] and refer subject as appropriate (i.e. Primary Care Provider or ER). Should an increase in neurologic impairment and/or abnormal clinical findings be noted, these are documented and coded according to type, location, severity, action(s) taken, and outcome. This procedure is in place in our studies for safety measures. This provision is important to detect new neurologic findings or conditions.

Internal Committee Monitoring

The internal committee consists of our consultant [redacted].

[redacted] is unblinded and will observe actual treatment sessions for quality control purposes (twice a year). He will prepare written reports on the administration of treatment protocols (Conditions 1, 2 and 3), summarize his observations on the quality control of the delivered intervention, but will not identify individual subjects or treatment arms.

[redacted] is blinded and will observe actual neuro/NST assessments for quality control purposes during site visits. She will review neuro documentation (notes) and symptom diaries for quality control purposes (two times a year for the 1st year and yearly thereafter for this purpose [5th year, her second visit for year 5 will include interpretation of pain outcomes]). She will prepare written reports on the neuro/NST and summarize her findings, but will not identify individual subjects or treatment arms.

Study Staff Regular Meetings

All members of the investigative team will meet regularly to discuss the operation and facilitation of the study. Monthly summaries of data status and edit/error checking reports are reviewed with the PI, statistician and data manager to insure continuous project monitoring. Case report forms are created for all instruments used in this study. An existing project management system in use at our facility is adapted to track recruitment, subject scheduling, subject tracking, visit attendance and data completeness.

Fidelity to Implementation of Intervention - Treatment Protocols

Strict operations procedures are implemented to ensure the replicability and consistency in administering protocol. All acupuncture sessions is monitored by the Study Facilitator to ensure proper implementation and fidelity to protocol sessions. The Treating Acupuncturists (TA) implement the Acu/Moxa protocol to subjects as determined by their condition assignment. The protocols for Conditions 1, 2 & 3 are outlined and detailed in our procedure manual. Sequencing and timing of points were tested in the PI's preliminary studies work. Protocols for each condition were refined and written under the direction of the investigative team.

Credentials, Requirements and Training

Dr. Joyce K. Anastasi (PI) has academic degrees in research (PhD), clinical practice (DrNP), and Traditional Chinese Medicine as an acupuncturist (Diplomate in Acupuncture, certified by the National Certification Commission for Acupuncture and Oriental Medicine and NYS Licensed Acupuncturist) which has prepared her to design and implement several NIH funded acupuncture/moxibustion randomized controlled clinical trials. Her research has focused largely on treatment protocols for managing symptoms related to chronic conditions (digestive and neurological). She has served on numerous boards for developing standards in acupuncture research and methodologies. She was was nominated, appointed and co-authored an Institute of Medicine (IOM) publication focusing on complementary and alternative medicine use by the American public and served on the revision committee for the Standards for Reporting Clinical Trials of Acupuncture (STRICTA). Dr. Anastasi completed several preliminary studies which have informed this research study proposal.

All acupuncture staff credentials have been verified. (Once Notice of Grant Award (NGA) is received the PI will forward biosketches, Citi Training dates and proof of NYS Licensure to Research Navigator for the IRB)

Required Credentials for TA: Graduated from an accredited acupuncture program (ACAOM); National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM) certified, New York State License to practice Acupuncture (LAc); minimum of 2 years of experience serving as research Treating Acupuncturist (following the research treatment protocol precisely as instructed).

Required Credentials for DA: Everything required of the TA with the addition of a minimum of 5 years practicing acupuncture using TCM principles. DAs are required to be assessed for TCM diagnostic competency (minimum 80% agreement and 85% accuracy). These figures represent 'almost perfect' agreement[81, 82] with excellent accuracy, and are commonly reported in the literature[83, 84].

Required Protocol Training: Prior to the implementation of the study, all Treating Acupuncturists attend an acupuncture point location training session, pass a written and practical exam on point locations (both traditional [true] and sham points) conducted by N. Dawes. They will *receive detailed instructions* regarding the implementation of acupuncture procedures/techniques for Conditions 1, 2, and 3 from N. Dawes and Dr. Anastasi. Current standards of practice are reviewed including cleansing the acupuncture site and proper disposal of needles.

Required Conduct - Note on TA and subject interaction – There is *no* discussion between the TA and the subject. This is to maintain the research milieu and to ensure consistency and uniformity of protocol

application. All questions and/or comments are directed to the *SF who is present during all treatment sessions*. Subjects are informed of this procedure at the time of consent. The SF role is otherwise scripted so that all subjects receive the same level of interaction.

In all of our acupuncture trials we developed carefully constructed training sessions and protocol manuals which include illustrations of traditional and sham point locations. According to Schnyer this method provides a way to deliver uniform, consistent and replicable treatments and procedures[85].

Required Study Facilitator (SF) Training: The SF will undergo training [redacted] with the study acupuncturists. [redacted] served as an SF in prior studies. While she has a degree in Oriental Medicine health sciences including acupuncture she will ***not*** treat in this study. [redacted] is CPR certified and has experience in monitoring quality control procedures, and facilitating such a trial. SF training emphasis is on subject safety, methodical facilitation of all Conditions, monitoring of protocols, timing and sequencing of points, keeping discussion to a minimum when treatments are in session, structured elicitation of adverse events, recording/documenting sessions, blinding procedures, unblinding subjects at final session and scheduling of post-study control subjects for true Acu/Moxa sessions. This training is done by Dr. Anastasi and [redacted]

[redacted]

All individuals associated with this research study having any form of contact with study subjects and/or identifiers will be added/uploaded to "Study Team Members" when we receive the Notice of Grant Award.

References

1. IASP. Painful HIV-Associated Sensory Neuropathy:Pain Clinical Updates. International Association for the Study of Pain 2010;13(3):1-8.
2. Farquhar-Smith P. Chemotherapy-induced neuropathic pain. Curr Opin Support Palliat Care 2011;5:1-7.
3. Bhatia NC, FC. Neurologica complications in treated HIV-1 infection. Current Neurology Neuroscience Rep 2016;16.
4. Chai NM, JC. HIV and peripheral neuropathy. In: Merlin J, Selwyn, PA, Treisman, GJ, Giovanniello, AG, editor. Chronic Pain and HIV: A Practical Approach. First Edition ed. NY, NY: John Wiley & Sons; 2016.
5. Shakher J, Stevens M. Update on the management of diabetic polyneuropathies. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2011;4:289-305.
6. de Sa e Benevides M, Filho, SB, Debona, R, Bergamaschi, ENC, Nunes, JC. Prevalence of peripheral neuropathy and associated factors in HIV-infected patients. Journal of the Neurological Sciences 2017;375:316-20.
7. Evans S, Ellis R, Chen H, et al. Peripheral neuropathy in HIV: prevalence and risk factors. AIDS 2011;25:919-28.
8. Wright E, Brew, B, Araywichanont, A, Robertson, K, Samintharpanya, K, Kongsaengdao, S, Lim, M, Vonthanak, S, Lal, L, Sarim, C, Huffam, S, Li, P, Imran, D, Lewis, J, Lun,WH, Kamarulzaman, A, Tau, G, Ali, ST, Kishore, K, Bain, MP, Dwyer, R, McCormack, G, Hellard, M, Cherry, C, McArthur, J, Wesselingh, S. Neurologic disorder are prevalent in HIV-positive outpatients in the Asia-Pacific region. Neurology 2008;71:50-56.
9. Ellis R, Rosario, D, Clifford, D, McArthur, J, Simpson, D, Alexander, T, Gelman, B, Vaida, F, Collier, A, Marra, C, Ances, B, Atkinson, J, Dworkin, R, Morgello, S, Grant, I. Continued high prevalence and adverse clinical impact of human immunodeficiency virus-associated sensory neuropathy in the era of combination antiretroviral therapy. Arch Neurology 2010;67(5):552-58.
10. Smyth K, Affandi, JS, McArthur, JC, Bowtell-Harris, C, Mijch, AM, Watson, K, Costello, K, Woolley, IJ, Price, P, Wesselingh, SL, Cherry, CL. Prevalence of and risk factors for HIV-associated neuropathy in Melbourne, Australia. HIV Medicine 2007;8:367-73.

11. Oshinaike O, Akinbami A, Ojo O, et al. Influence of age and neurotoxic HAART use and frequency of HIV sensory neuropathy. AIDS Research and Treatment 2012.
12. Wang S, Ho, EL, Grill, M, Lee, E, Peterson, J, Robertson, K, Fuchs, D, Sinclair, E, Price, RW, Spudlich, S. Peripheral neuropathy in primary HIV infection associates wttish systematic and central nervous system immune activation. Journal Acqured Immune Deficiency Syndrome 2014;66:303-10.
13. Lee A, Bosch, RJ, Evans, SR, Wu, K, Harrison, T, Grant, P, Clifford, DB. Patterns of peripheral neuropathy in ART-naive patients initiating modern ART regimen. Journal of Neuro Virology 2015;21:210-18.
14. Evans S, Simpson, DM, Kitch, DW, King, A, Clifford, DB, Cohen, BA, McArthur, JC. A randomized trial evaluating prosaptide for HIV-associated sensory neuropathies: Use of an electronic diary to record neuropathic pain. PLoS One 2007;2(7):e551.doi:10.1371/journal.pone.0000551.
15. Dorsey SG, Morton PG. HIV peripheral neuropathy. AACN Clinical Issues 2006;17(1):30-36.
16. Bruce R, Merlin, J, Lum, P, Ahmed, E, Alexander, C, Corbett, A, Foley, K., Leonard, K, Treisman, GJ, Selwyn, P. 2017 HIVMA of IDSA Clinical Practice Guideline for the Management of Chronic Pain In Patients Living With HIV. Clinical Infectious Diseases 2017.
17. Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for report randomized trials: explanation and elaboration. Annals of Internal Medicine 2001;134:663-94.
18. Macpherson H, Altman DG, Hammerschlag R, et al. Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): extending the CONSORT statement. Acupuncture in Medicine 2010;28(2):83-93.
19. Nicholas P, Voss J, Wantland D, et al. Prevalence, self-care behaviors, and self care activities for peripheral neuropathy symptoms of HIV/AIDS. Nursing and Health Sciences 2010;12:119-26.
20. Lee K, Vivithanaporn P, Siemieniuk R, et al. Clinical outcomes and immune benefits of anti-epileptic drug therapy in HIV/AIDS. BMC Neurology 2010;10:1-11.
21. Phillips T, Brown, M, Ramirez, JD, Perkins, J, Woldeamanuel, YW, Williams, ACD, Orengo, C, Bennett, DLH, Bodi, I, Cox, S, Maier, C, Krumova, EK, Rice, ASC. Sensory, psychological, and metabolic dysfunction in HIV-associated peripheral neuropathy: A cross-sectional deep profiling study. Pain 2014;155:1846-60.
22. Stavros. L & Simpson D. Understanding the etiology and management of HIV-associated peripheral neuropathy. Current HIV/AIDS Rep 2014;11:195-201.
23. Mann R, Sadosky, A, Schaefer, C, Baik, R, Parsons, B, Nieshoff, E, Stacey, BR, Tuchman, M, Nalamachus, S. Burden of HIV-related neuropathic pain in the United States. Journal of International Association of Providers of AIDS Care 2016;15(2):114-25.
24. Simpson D. Diagnosing and managing peripheral neuropathy in HIV disease. Princeton: Bristol-Myers Squibb; 1998.
25. Dorsey S, Morton, PG. HIV Peripheral Neuropathy Pathophysiology and Clinical Implications. AACN Clinical Issues 2006;17(1):30-36.
26. Starkweather A, Heineman, A, Storey, S, Rubia, G, Lynon, D, Greenspan, J, Dorsey, SG. Methods to measure peripheral and central sensitization using quantitative sensory testing: A focus on individuals with low back pain. Applied Nursing Research 2016;29:237-41.
27. Nicholas P, Kemppainen, J., Holzmer, W., Nokes, K., Sanzero, E., Corless, I., Bunch, E., Bain, C., Kirksey, K., Davis, S., Goodroad, B. Self-care management for neuropathy in HIV disease. AIDS Care 2002;14(6):763-71.
28. Carpenter C, Fischl, MA, Hammer, SM, Hirsch, MS, Jacobson, DM, Katenskin, DA, Montainer, JS, Richman, DD, Saag, MS, Schooler, RT, Thompson, MA, Vella, S, Yeni, PG, Volberding, PA. Antiretroviral therapy for HIV infection in 1996: Recommendations of an international panel. JAMA 1996;272(2):146-54.
29. Jourjy J, Dahl, K, Huesgen, E. Antiretroviral treatment efficacy and safety in older HIV-infected adults. Pharmcotherapy 2015;35(12):1140-51.
30. Anastasi JK, Smolowitz J, Capili B. Distal sensory peripheral neuropathy in HIV: A case report. Clinical Scholars Review 2009;2(1):13-18.
31. Mizutani J. Practical moxibustion therapy. North American Journal of Oriental Medicine 1999(November):1-47.
32. Flaws B, Sionneau, P. The treatment of modern western medical diseases with Chinese medicine: A textbook and clinical manual. Boulder: Blue Poppy Press; 2001.

33. Galantino M, Eke-Okoro, S., Findley, T., Condoluci, D. Use of non-invasive electroacupuncture for the treatment of HIV-related peripheral neuropathy: A pilot study. The Journal of Alternative and Complementary Medicine 1999;5(2):135-42.
34. Tosches W, Cohen, C., Day, J. A pilot study of acupuncture for the symptomatic treatment of HIV associated peripheral neuropathy (PN). Paper presented at: International AIDS Conference; July 19-24, 1992; Amsterdam, Netherlands.
35. Goh M. Acupuncture as a treatment for peripheral neuropathy. Paper presented at: World Federal Acupuncture Society Conference, 1990; Paris.
36. Shlay J, Chaloner, K., Max, M., Flaws, B., Reichelder, P., Wentworth, D., Hillman, S., Brizz, B., Cohn, D. Acupuncture and amytriptyline for pain due to HIV-related peripheral neuropathy. JAMA 1998;11(18):1590-95.
37. Kaptchuk T. Acupuncture and amitriptyline for HIV-related peripheral neuropathic pain [Letters]. JAMA 1999;281(14):1270-72.
38. Anastasi JK, Capili B, McMahon DJ, Scully C. Acu/Moxa for Distal Sensory Peripheral Neuropathy in HIV: A Randomized Control Pilot Study. Journal of the Association of Nurses in AIDS Care 2013;24(3):268-75.
39. Dimitrova A, Murchison, C, Oken, B. Acupuncture for the treatment of peripheral neuropathy: A systematic review and meta-analysis. Journal of Alternative and Complementary Medicine 2017;23(3):164-79.
40. Vollmer M, Svetkey L, Appel L, et al. Recruitment and retention of minority participants in the DASH controlled feeding trial. Ethnicity Diseases 1998;8:198-208.
41. Fleiss JL. The design and analysis of clinical experiments. New York: John Wiley & Sons; 1986.
42. National Acupuncture Foundation. Clean needle technique manual for acupuncturists. A manual: Guidelines and standards for the clean and safe practice of acupuncture. 5th ed; 2004.
43. Beijing College of Traditional Chinese Medicine SCoTCM, Nanjing College of Traditional Chinese Medicine. Chinese Acupuncture & Moxibustion. Beijing: Foreign Languages Press; 1987.
44. Zhang X. Clinical observation on acupuncture and moxibustion treatment of peripheral nervous lesion caused by diabetes: Reports from China. Acupuncture & Moxibustion Research 1999;24(3):236-37.
45. Wolfe H. One approach to acumoxa therapy for pain due to tendonitis of the hand, wrist and forearm. American Journal of Acupuncture 1995;23(3):219-30.
46. Guerra J, Bassas, E, Andres, M, Verdugo, F, Gonzalez, M. Acupuncture [and moxibustion] for soft tissue shoulder disorders: A series of 201 cases. Acupuncture in Medicine 2003;21(1-2):18-22.
47. Lu Z, Dong, X, Zhang, T, Cao, W, Deng, Y. Relation between the therapuetic effect of moxibustion in treating arthralgia and SP and enkephalin in nervous tissues. Journal of Chinese Medicine 1989;9(1):69-74.
48. Maciocia G. The practice of Chinese medicine. New York: Churhill Livingston; 1994.
49. Ross J. Acupuncture point combinations: The key to clinical success. New York: Churchill Livingstone; 1995.
50. Deadman P, Al-Khafaji, M. A manual of acupuncture. Ann Arbor: Cushing Malloy, Inc.; 1998.
51. Hammerschlag R. NIH consensus development conference on acupuncture. Methodological and Ethical Issues in Acupuncture Research 1997:p.45-49.
52. Vincent CA. A controlled trial of the treatment of migraine by acupuncture. Clinical Journal of Pain 1989;5(4):305-12.
53. Birch S, Hammerschlag R, Trinh K, Zaslawski C. The non-specific effects of acupuncture treatment: When and how to control for them. Clinical Acupuncture and Oriental Medicine 2002;3:20-25.
54. Vincent C, Lewith G. Placebo controls for acupuncture studies. Journal of the Royal Society of Medicine 1995;88(4):199-202.
55. Kaptchuk T. Placebo needle for acupuncture. The Lancet 1998;352(September):992.
56. Pakenham K, Dadds M, Lennon H. The efficacy of psychosocial intervention for HIV/AIDS caregiving dyads and individual caregivers: A controlled treatment outcome study. AIDS Care 2002;14(6):731-50.
57. Naar-King S, Lam P, Wang M, et al. Brief report: Maintenance of effects of motivational enhancement therapy to improve risk behaviors and HIV-related health in a randomized controlled trial of youth living with HIV. Journal of Pediatric Psychology 2008;33(4):441-45.
58. Simpson D, Olney, R, McArthur, JC, Khan, A, Godbold, J, Ebel-Frommer, K. A placebo-controlled trial of lamotrigine in adult subjects with painful HIV-associated neuropathy. Neurology 2000;54:2115-19.

59. McArthur J. The reliability and validity of the subjective peripheral neuropathy screen. JANAC 1998;9(4):84-94.
60. Simpson D, Dorfman, D, Olney, MD, McKinley, G, Dobkin, J, So, Y, Berger, J, Ferdon, MB, Friedman, B. Peptide T in the treatment of painful distal neuropathy associated with AIDS: Results of a placebo controlled study. Neurology 1996;47:1254-59.
61. Simpson D, McArthur, JC, Olney, R, Clifford, D, So, Y, Ross, D, Baird, BJ, Barrett, P, Hammer, BS, Lamotrigine HIV Neuropathy Study Team. Lamotrigine for HIV-associated painful sensory neuropathies: A placebo-controlled trial. Neurology 2003;60:1508-14.
62. McArthur J, Yiannoutsos, C, Simpson, DM, Adornato, BT, Singer, EJ, Hollander, H. A phase II trial of nerve growth factor for sensory neuropathy associated with HIV infection. Neurology 2000;54:1080-88.
63. Evans SR, Clifford DB, Kitch DW, et al. Simplification of the research diagnosis of HIV-associated sensory neuropathy. HIV Clinical Trials 2008;9(6):434-39.
64. Gracely R, McGrath, P, Dubner, R. Ratio scales of sensory and affective verbal pain descriptors. Pain 1978;5:5-18.
65. AHRQ. Assessment and management of chronic pain. www.guideline.gov ed: Agency for Healthcare Research & Quality. NGC-7602; 2009. p. 1-91.
66. Leucht S, Engel, RR. The relative sensitivity of the clinical global impression scale and the brief psychiatric rating scale in antipsychotic drug trials. Neuropyschopharmacology 2006;31:406-12.
67. Whitehead WE, Corazziari E, Prizont R, Senior J, Thompson D. Definition of a responder in clinical trials for functional gastrointestinal disorders: Report on a symposium. In: Drossman DA, editor. ROME II: The Functional Gastrointestinal Disorders. 2nd ed. McLean: Degnon Associates; 2000.
68. Gencoz F, Gencoz, T, Soykan, A. Psychometric properties of the Hamilton Depression Rating Scale and other physician-rated psychiatric scales for the assessment of depression in ESRD patients undergoing hemodialysis in Turkey. Psychology, Health & Medicine 2007;12(4):450-59.
69. Pereira N, Jansen, SJ, Raskin, KA, Hornicek, FJ, Ferrone, ML, Shin, JH, Bramer, JAM, van Dijk, CN, Schwab, JH. Most efficient questionnaires to measure quality of life, physical function and pain in patients with metastatic spine disease: A cross-sectional prospective survey study. The Spine Journal 2017;17:953-61.
70. Badia X, Podzamczer D, Garcia M, et al. A randomized study comparing instruments for measuring health-related quality of life in HIV-infected patients. AIDS Patient Care 1999;13:1727-17-35.
71. Henderson W, Schlenk E, Kim K, et al. Validation of the MOS-HIV as a measure of health-related quality of life in persons living with HIV and liver disease. AIDS Care 2010;22(4):483-90.
72. Gifford A, Laurent, DD, Gonzalez, VM, Chesney, MA, Lorig, KR. Pilot randomized trial of education to improve self-management skills of men with symptomatic HIV/AIDS. Journal of Acquired Immune Deficiency Syndrome & Human Retrovirology 1998;18(2):136-44.
73. Mathews WC, McCutchan, J.A., Asch, S., Turner, B.J., Gifford, A.L., Kuromiya, K., Brown, J., Shipiro, M.F., Bozzette, S.A. National estimates of HIV-related symptom prevalence from the HIV cost and services utilization study. Medical Care 2000;38(7):750-62.
74. Borkovec TD, Nau SD. Credibility of analogue therapy rationales. Journal of Behavioral Therapy & Experimental Pyschiatry 1972;3:257-60.
75. Folstein MF, Folstein, S. E. & McHugh, P. R. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research 1975;12(3):189-98.
76. Alosh MH, MF. A flexible strategy for testing subgroups and overall population. Statistics in Medicine 2009;28(1):3-23.
77. Heitjan DF. Annotation: what can be done about missing data? Approaches to imputation. [letter; comment.]. American Journal of Public Health 1997;87(4):548-50.
78. SAS. SAS computer program, Release 9.0. Cary, North Carolina: SAS Institute; 1989.
79. Grady C. Payment of clinical research subjects. The Journal of Clincal Investigation 2005;115(7):1681-87.
80. Grady C, Dickert N, Jawetz T, Gensler G, Emanuel E. An analysis of U.S. practices of paying research participants. Contemporary Clinical Trials 2005;26:365-75.
81. Landis JH, Koch, G.G. The measurement of observer agreement for categorical data. Biometrics 1977;33:159-74.
82. Fleiss JL. Statistical methods for rates and proportions. 2nd ed. New York: John Wiley & Sons; 1981.

83. Lipton RB, Dodick, D., Sadovsky, K., Endicott, J., Hettiarachchi, J., Harrison, W.,. A self-administered screener for migraine in primary care: The ID Migraine validation study. Neurology 2003;61(3):375-82.
84. Marder K, Albert, S.M., McDermott, M.P., McArthur, J.C., Schifitto, G., Senes, O.A., Sacktor, N., Stern, Y., Palumbo, D., Kieburtz, K., Cohen, B., Orme, C., Epstein, L.G. Inter-rater reliability of clinical staging of HIV associated cognitive impairment. Neurology 2003;60(9):1467-73.
85. Schnyer RN, Allen, J.B. Bridging the gap in complementary and alternative medicine research: Manualization asa means of promoting standardization and flexibility of treatment in clinical trials of acupuncture. The Journal of Alternative and Complementary Medicine 2002;8(5):623-34.