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Acupuncture/Moxibustion RCT for Distal Sensory Peripheral Neuropathy in HIV/AIDS:

Rationale, Design, Methods, Procedure and Logistics

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Abstract

Distal sensory peripheral neuropathy is a common neurological complication experienced by people living with the human immunodeficiency virus (HIV). Traditional Chinese medicine (TCM) may offer effective interventions in the management of its symptoms. To improve the quality and transparency of reporting acupuncture clinical trials, the Consolidated Standards of Reporting Trials (CONSORT) guidelines were developed in 1996 and the Standards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA) recommendations were introduced in 2001. Incorporating international guidelines, this paper describes the development of a RCT including rationale, design, methods, procedures and logistics for a pilot study aimed at evaluating acupuncture and moxibustion for neuropathy associated with HIV. Using STRICTA guidelines as a template, aspects of clinical research design are explored to further optimise future studies of TCM.

Keywords

Acupuncture; moxibustion; peripheral neuropathy; HIV; research; clinical trial

Background

Since the mid 1990s, the morbidity and mortality associated with the human immunodeficiency virus (HIV) have been reduced with the introduction of highly active

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antiretroviral therapy (HAART). HAART regimens are now an integral part of living with HIV; treatments used to manage the disease have been associated with complicating the disease process (Keswani, Pardo, Cherry, Hoke, McArthur, 2002), causing many unfavourable side/adverse effects and negatively impacting quality of life (Lorenz, Shapiro, Asch, Bozzette, Hays, 2001). Although HAART is effective in controlling the virus, distal sensory peripheral neuropathy (DSP) continues to be a prevalent problem (Nicholas et al., 2002; Stawzewski et al., 1998; Whalen, Antani, Carey, Landefeld, 1994). Treatments prescribed to manage the pain associated with DSP are largely ineffective (Simpson et al., 2002), with side effects and increased risk for drug interactions in combination with antiretroviral combination therapies (Preston et al., 1998; Treisman & Kaplina, 2002).

An estimated 30 to 35 per cent of persons with HIV are diagnosed with peripheral neuropathy that causes pain, dysesthesias and reduced quality of life (CDC, 1993; Griffin et al., 1991; Nicholas et al., 2002; Schifitto et al., 2002; Shlay et al., 1998; Simpson 1998). The pathogenesis associated with DSP in HIV remains unknown. Proposed mechanisms include cytokine dysregulation, viral protein produced neurotoxicity and mitochondrial dysfunction secondary to the use of dideoxynucleoside antiretroviral medications (eg, didanosine, stavudine or d4T) (Gonzalez-Duarte, Cikurel, Simpson, 2007; Simpson, Estanislao, Brown, 2008; Simpson et al., 1998). Treatments to manage the symptoms of DSP have largely focused on pharmacologic therapy, such as non-narcotic and narcotic analgesics, antidepressants and anticonvulsants (Keswani et al., 2002; Simpson & Tagliati 1994). Placebo-controlled trials have found these agents to be limited in efficacy for managing the symptoms of DSP (Schifitto et al., 2006; Silver, Blum, Grainger, Hammer, Quessy, 2007).

For this study, we have chosen to examine the use of a traditional Chinese medicine (TCM) approach, namely acupuncture/moxibustion (Acu/Moxa), to reduce pain severity and decrease associated symptoms of DSP (‘pins and needles’ sensation, numbness) in HIV. Acupuncture is a treatment modality commonly used by individuals with HIV to manage symptoms associated with the disease and as an adjunctive therapy to manage pain (Lin & Chen, 2009; WHO, 2003). Several studies have reported supportive evidence on the use of acupuncture for conditions such as Raynaud’s syndrome (Appiah, Hiller, Caspary, Alexander, Creutzig, 1997), facial pain (Novak, 2000), migraine prophylaxis (Allais et al., 2002), chronic neck pain (Nabeta & Kawakita, 2002) and cancer pain (Alimi et al., 2003). Additional studies have assessed the use of moxibustion for the treatment of other types of painful conditions, including peripheral neuropathy in diabetes (Zhang, 1999), soft tissue shoulder disorders (Guerra, Bassas, Andres, Verdugo, Gonzalez, 2003) and arthralgia (Lu, Dong, Zhang, Cao, Deng, 1989). However, well-designed, randomised, controlled, blinded studies on acupuncture and moxibustion for DSP in HIV are lacking. The Standards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA) (MacPherson et al., 2002) and Consolidated Standards of Reporting Trials (CONSORT) (Altman et al., 2001) were used as a guide in the development and design of this study (see Table 1). This paper describes our methodology.

Design

This study is a prospective, randomised, sham/placebo controlled, subject- and evaluator-blinded, parallel-groups clinical trial. Adult men and women diagnosed with HIV and DSP are randomised to one of two groups, true acupuncture/moxibustion (Acu/Moxa) or sham acupuncture/placebo moxibustion (sham Acu/placebo Moxa) control. After completing a screening/intake session, randomised subjects begin a series of twelve treatment sessions (twice-weekly for six weeks) followed by three non-treatment follow-up sessions at weeks 9, 11 and 15. A twice-weekly treatment schedule was selected based on the experience of our research team, consensus of our clinical acupuncturists, advice of a patient consultant (HIV-positive individual) and a needs assessment with HIV individuals with DSP. The treatment schedule selected for this study closely reflects acupuncture practice. The three non-treatment follow-up sessions were included to provide data to assess longer-term effects of the Acu/Moxa treatment for DSP.

Rationale for Combination Acu/Moxa Therapy

According to TCM theory, peripheral neuropathy tends to be a root deficiency of *qi* and *yin* with a branch excess of blood stagnation, dampness and/or damp heat impediment (Flaws & Sionneau, 2001). Acupuncture alone is not considered the standard of care for this condition (Flaws & Sionneau, 2001). Based on TCM theory, pathogenesis, diagnoses and treatment principles for the pattern differentiation of DSP, the Acu/Moxa treatment protocol utilised for this study is thought to be the optimal method for this syndrome (see Table 1 STRICTA, item 1b for TCM diagnostic groupings). The component effects of Acu and Moxa are considered synergistic and it is this combined benefit that the study has been designed to detect. A recognised flaw in many clinical trials assessing efficacy of complementary and alternative medicine (CAM) is the dissociation of treatment components that appear together in traditional usage. This trial was designed to follow the recommendation that ‘in studies of a system of traditional medicine to treat a specific disease, the investigators consider the system as a whole, instead of a single core modality’ (Nahin & Straus, 2001, p.162).

Study participants

The study sample consists of 50 men and women, 18 years of age or older, diagnosed with HIV. Study participants have pain associated with symptoms of HIV-related lower extremity DSP, verification from their primary care provider (PCP) of HIV status, DSP diagnosis and clinical suitability for the study. Their completed baseline Symptom Diary (SD) will indicate at least ‘moderate’ severity of pain based on the Gracely Pain Scale, and they will score 24 or better on the Mini Mental Status Examination (M. Folstein, S. Folstein, McHugh, 1975). Individuals taking antiretroviral agents must be on a stable regimen (same drug(s), dose & frequency) for at least eight weeks prior to study entry. Analgesic and/or other medications, which may have neuropathy as a side effect, must be taken as a stable regimen for at least 21 days prior to enrollment. Full inclusion and exclusion criteria are presented in Table 2.

Procedures

Recruitment and Preliminary Telephone Screening

Institutional review board approval was received by the conducting academic health science centre. To reflect the demographics of an urban HIV/AIDS population, subjects are recruited from flyers/brochures posted in HIV community-based agencies, paid advertisements in newspapers/magazines, health fairs specific to HIV care, and referrals from HIV PCPs (physicians, nurse practitioners and physician assistants) throughout New York City's five boroughs. Potential subjects initiate the inquiries for this study and are telephone-screened by a research coordinator to determine preliminary eligibility. Based on their self-reported medical history, if a potential subject meets the criteria, a Release of HIV and Medical Information form is sent to that person's mailing address to obtain their authorisation for the research team to contact their HIV PCP to confirm HIV status, medical history, DSP diagnosis, and the PCP's agreement of study suitability. Potential subjects determined to be eligible are provided an overview of the study and informed that they will attend a series of sessions at the research centre, complete health related questionnaires at specific time points, and record their symptoms in a daily SD for the duration of the study, if they are enrolled into the study. Compensation for participation is discussed. Subjects receive $10 USD for each session completed during visits 1 through 14, and $20 USD for the completion of visits 15 and 16. A $4 USD MetroCard is also provided to cover round trip bus/subway transportation for each study visit.

Session 1: Screening/Intake Session—A screening/intake session is scheduled once written verification of medical history is received from the potential subject's PCP. During the intake session, the informed consent process is initiated. A thorough description of the study details, requirements and time for questions are provided prior to signing the consent form.

Once the consent form is signed, subjects undergo a neurological assessment from a nurse practitioner (NP) with a specialty in neurology. The assessment includes skin inspection for colour, temperature, hair distribution and lesions, as well as assessments of the peripheral vascular system of the lower extremities, cranial nerves II to XII, motor pathway and sensory pathway (including filament sensory testing), reflex arc, gait and coordination. Baseline questionnaires are administered and a one-week SD is given to subjects to establish the baseline symptom severity for study eligibility.

Subjects are informed that the research team reviews their questionnaires prior to study enrolment and randomisation. Should the study team identify clinical information contained in the SD, General Health History Form and/or the neurological assessment that requires further clarification, enrolment may be delayed until the clinical situation can be accounted for, and/or treated. When considered necessary, subjects are referred to their PCP for further evaluation and management. All enrolment forms and general health history information are reviewed by the principal investigator and neurology staff for study clearance prior to enrolment.

Session 2: Eligibility, Randomisation, Treatment Sessions—Subjects bring in their completed one-week SD to determine whether they meet enrolment criteria by demonstrating an average of at least ‘moderate’ severity on the Gracely Pain Scale. Eligible subjects are randomised to one of two study conditions by the method of randomly permuted blocks. This method allocates subjects to treatment in a manner that ensures equal allocation of subjects among treatment conditions at the end of each block. Assignment blocks of different sizes (2, 4 or 6 assignments) are randomly intermingled to eliminate the basis for guessing the next treatment assignment (Fleiss, 1986).

The principal investigator, co-investigators, statistician, NP neurology specialists, study coordinator, and data manager are blinded to treatment assignment until the final statistical analysis. Only the study facilitator (SF), acupuncturists, and the clinical acupuncture consultant are not blinded. The SF is present at all treatment sessions and monitors each session for protocol fidelity and written documentation of protocol administration (ie, procedures, points, sequencing). The acupuncturists are given the assigned treatment condition (Acu/Moxa or Sham Acu/Placebo Moxa) by the SF. The clinical acupuncture consultant performs the training and testing of the acupuncturists to enhance uniformity in conduct of the study, as well as observes treatment sessions for quality control.

All treatment sessions last one hour. Forty minutes is allocated for the treatment and the remaining time is allowed for undressing and re-dressing post treatment. An additional 15 minutes is allotted for sessions that require the completion of instruments/questionnaires. Also, at each session prior to treatment, all subjects complete a Symptom Checklist and the SF asks subjects open-ended questions regarding adverse events or healthcare visits to a provider. The questions are, “Have you had any health problems since your last study visit?” and, “Have you seen a healthcare provider since your last study visit?” Responses to the Symptom Checklist or open-ended questions that may indicate an adverse event are followed with additional questions to gather necessary information to assess the clinical scenario and to generate a written report.

Follow-up Sessions

At weeks 9, 11 and 15, subjects bring in their SD, complete questionnaires/forms, have a neurological assessment and are provided compensation fees. No treatments are given during these follow-up sessions. At the end of the final follow-up (week 15), the SF unmasks the subject to their treatment assignment. Subjects assigned to the control group are offered twelve true Acu/Moxa treatments at no charge. To preserve blinding fidelity, the SF has a dedicated telephone line and voice mail for ‘completed’ subjects who were assigned to the control group, as the SF is responsible for scheduling post-study control appointments after unblinding. Post-study control subjects are also treated away from the study area to preserve blinding for the study staff.

General Procedures

All acupuncture and moxibustion procedures, true or sham/placebo, are performed by licensed acupuncturists trained in TCM. All acupuncturists completed training sessions and

passed a written and practical point location examination specific to the protocol, prior to joining the study team.

All acupuncture procedures are performed with one-inch Seirin®, J-type, No. 2 (0.18) × 30mm, 38 gauge sterile, single use, disposable needles. Needles are not shared between patients or on different points on the same patient and all procedures are performed according to the guidelines and standards in *Clean Needle Technique for Acupuncturists*, a manual by the National Acupuncture Foundation (NAF) (National Council of Certified Acupuncturists, 1989). Both true and placebo moxibustion procedures are performed with lit moxa sticks made from the dried leaves of Artemisia Vulgaris, purchased from one commercial medical supplier. Acupuncture points are stimulated with lighted moxa sticks using the indirect technique (Liangyue et al., 1993). All treatment sessions follow a specific regimen which includes sequenced acupuncture point needle insertion, fixed needle indwell time and monitored per protocol conditions. All subjects, regardless of their group assignment, are blindfolded during treatment sessions and all subjects follow the same study schedule.

CONDITION 1: Acupuncture/Moxibustion

Acupuncture—Subjects receive point stimulation, *de qi* (termed 'receiving *qi*') at traditional point locations (Liangyue et al., 1993). The needling method used in Condition 1 is called the reinforcing/tonification method and performed by inserting the needle at the appropriate depth, per classic text, when the patient exhales. After insertion of the needle, it is rotated nine times gently and slowly with small amplitude in a clockwise direction. An expert panel of acupuncturists have reviewed and participated in the selection of points, sequencing and timing of this protocol.

Moxibustion—All procedures are performed according to standard indirect moxibustion techniques as described in the classic text, *Chinese Acupuncture & Moxibustion* (Liangyue et al., 1993). A burning moxa pole is held approximately one inch over the acu-points and moved in a clockwise circular motion directly over the point (Liangyue et al., 1993). Each acu-point is stimulated for two minutes. This method provides gentle warming without intense concentration of heat.

CONDITION 2: Sham Acupuncture/Placebo Moxibustion [1,2]

For both ethical and methodological reasons (Cook & Campbell, 1979), it is important that subjects randomised to the control group perceive their experience to be as valuable as subjects in the active treatment group. A lack of perceived value in the control group could lead to differential attrition across conditions that would jeopardise interpretability of study results. We also suspect that experiential cues accompanying acupuncture and moxibustion may impart significant but transient placebo responses. Therefore we believe that the best methodological approach is to expose control subjects to sham Acu/placebo Moxa that is indistinguishable from true Acu/Moxa. The technique and location(s) used for

[1]All sham point locations are anatomically specific and are diagrammed in our procedure manual.
[2]The sequence and timing of treatment protocol are the same for Conditions 1 and 2.

administration of sham Acu/placebo Moxa are distinct from that of Condition 1. An important concern in designing this study was the selection of procedures that would maximise experimental control over non-specific confounding factors.

Sham Acupuncture—Subjects receive sham acupuncture using superficial needling at non-acupuncture points according to previously established procedures (Birch, Hammerschlag, Trinh, Zaslawski, 2002; Hammerschlag, 1997; Vincent, 1989). These points are 2–3 cm away from the true point location (in predetermined locations that are not on a channel/meridian) with an insertion depth of 1–2 mm, which is just sufficient to make the needle stand vertically, without eliciting a *de qi* response. This procedure 'minimizes the specific effects of the needling while maintaining its psychological impact' (Vincent & Lewith, 1995, p.200). This method has been assessed as a credible and effective control procedure (Vincent, 1989). Use of controls in acupuncture is controversial. However, we have employed all of the suggested recommendations to minimise the physiological effects, yet maintain the psychological impact using the sham needling technique (Vincent, 1989).

Placebo Moxibustion—A burning moxa stick is held approximately 8 inches above and 2–3 cm away from the true point location for a period of two minutes. The acupuncturists are trained and instructed to administer this procedure in a manner that does not generate any heat sensation. The acupuncturist intermittently places her/his hand close to the subject's skin to assess heat sensation. This allows the 'moxa-naïve', blindfolded subjects to experience the smell, but not the heat of the burning herb.

Unlike the well-established research 'sham' condition of acupuncture (Hammerschlag, 1997), moxibustion does not have a well-established control. We assessed the credibility of our placebo moxa procedure in a study with 40 moxa-naïve, healthy adults randomly assigned to True Moxa or Placebo Moxa, and blindfolded for the study session. The demographic characteristics of the two groups did not differ statistically. No statistically significant between-group difference was found on any of the five credibility questions (Borkovec & Nau, 1972) when tested with a 2-sample median test: (Q1) Logic of treatment, p=0.53; (Q2) Success of treatment in alleviating symptoms, p=0.97; (Q3) Confident that this was a true treatment p=0.81; (Q4) Would recommend this form of treatment to a friend, p=0.81; (Q5) Likelihood of seeking care from a CAM practitioner in the future, p=0.80.

Outcome Measures

All measures were pre-tested on subjects with similar characteristics to the proposed study participants to ensure that the instruments would be appropriate for this population.

Symptom Diary (SD)—To provide a multi-dimensional picture of DSP, the daily Symptom Diary (SD) contains three self-report measures: the Gracely Pain Scale (GPS), the Subjective Peripheral Neuropathy Screen (SPNS) and a dermatome chart allowing a localised report of type of sensation, intensity, and duration.

Gracely Pain Scale (GPS)—The GPS is a Likert-type measure of the sensory components of pain using a magnitude ratio scale, widely used to provide a quantifiable

outcome for studies of DSP associated with HIV by focusing on the pain sensation (McArthur, 1998; Simpson et al., 2000; Simpson et al., 1996). Subjects are instructed to rate their pain due to DSP by selecting one of 13 words that most appropriately describes their average and their worst pain. Each verbal descriptor corresponds to a log-scaled value ranging from 'nothing' (0.00) to 'extremely intense' (1.77). Weekly average of log-converted scores will be used for the primary analysis. The GPS has demonstrated strong reliability and validity of the ratio scales for verbal sensory descriptors (Gracely, McGrath, Dubner, 1978), between-group (r = 0.97), within sessions (r = 0.99) and between experiments (r = 0.99).

Subjective Peripheral Neuropathy Screen (SPNS)—SPNS is a brief self-reporting screening tool for DSP pain severity and type used to evaluate patients with HIV for sensory neuropathy (McArthur, 1998). Subjects choose between aching/burning, 'pins and needles', or numbness to describe the type of pain symptom. Subjects record severity of neuropathy symptoms and whether the symptom occurs on the hands/arms or on the feet/legs; severity is rated on a 10-point scale. Two sub-scores, Average Severity Score (ASS) and Clinical Severity Grade (CSG) will be computed for analyses. ASS is the mean daily symptom severity score ranging from mild (1) to most severe (10). CSG is derived from the highest symptom severity score of any symptom such that the maximum severity scores of 0, 1–3, 4–6, and 7–10 are assigned a severity grade of 0, 1, 2, and 3, respectively. The SPNS is also a valid tool to track and monitor antiretroviral neurotoxicity, evidenced by highly significant Spearman's rank difference correlations between the neurological exam severity grade and the ASS (rs = 0.65), and the CSG (rs = 0.65) (McArthur, 1998). The construct validity is assessed by comparing the results between HIV-positive patients diagnosed with neuropathy and HIV-positives without neuropathy using t-tests. Between-group comparisons show that both SPNS sub-scores, ASS and CSG, could discriminate among HIV-positive patients that are likely to experience neuropathy and those that are likely to have little or no symptoms (McArthur, 1998). Cronbach's alpha yields a reliability of 0.86 for the six symptoms of the SPNS.

Body Diagram Dermatone Chart—This dermatome-based diagram permits tracking of the spatial progression of DSP symptoms and is incorporated into Symptom Diary. Subjects mark the location of symptoms on an image depicting five dermatomes on both the front and back lower extremities. Dermatomes represent specific regions of nerve reception of sensory impulses. Subjects record on each diagram the type, intensity and duration of DSP sensation.

Additional Information Recorded in the Symptom Diary—Daily symptom severity is recorded on a 37-item scale that rates symptoms from 'not present' (0) to 'extreme' (4). Symptoms listed include, but are not limited to, abdominal pain, bloating, joint pain, muscle pain, irritability and headache. Subjects record daily antiretroviral combination therapy and all other medications taken. Name(s), dose, frequency, and time and date taken are recorded in the columns provided. Questions for each day prompt for a declaration of any missed doses. If there is a change in medications, subjects are to record those changes in the diary and inform the study staff. For menstruating female subjects, dates, duration and heaviness of menstrual flow is recorded in the diary.

Clinical Global Impression Scale (CGIS)—This scale, administered pre-intervention, during, and post intervention, measures illness severity separately from global improvement on Likert-type scales with seven descriptors. The global severity of symptoms scale measures the subject's level of discomfort with his/her DSP, from no discomfort (0) to very severe discomfort (6) (Whitehead, Corazziari, Prizont, Senior, Thompson, 2000). The global improvement scale measures the level of change after receiving an intervention, from 'no improvement at all' (0) to 'great improvement' (6). The score allows for the integration of a disparate group of symptoms into a single global clinical rating.

Neurological Assessment Form—The neurological assessment form provides a systematic approach to a thorough neurological evaluation, including blood pressure, pulse rate, skin colour, moisture, temperature, texture and lesions, nail-bed colour, lower leg hair distribution, lower extremity size, symmetry, oedema, venous pattern and peripheral pulses and cranial nerves II to XII. Also included are assessments of motor pathway, sensory pathway, gait, coordination, reflex arc, thermal, deep pain, light touch, filament testing and vibration. Anterior and posterior diagrams of the body, with outlined dermatomes, are included to record the location of relevant findings. The neurological assessments are conducted by a NP neurology specialist and reviewed by the neurology staff.

Quality of Life—The Medical Outcome Study Short-Form Survey-36 (MOS-SF-36) is sensitive for measuring health status in patients with HIV infection (Ware & Sherbourne, 1992). This measure is used to determine physical functioning and health status from the subject's point of view. The instrument consists of 36 questions measuring limitations in physical activities or usual role activities because of health problems, limitations in social activities because of physical or emotional problems, bodily pain, mental health, limitations in usual role activities because of emotional problems, vitality and general health activities (Ware, 1997). Cronbach alpha reliability of 0.86 is reported for patients with HIV. Construct and discriminant validity are also indicated. Patients with HIV have significantly lower scores than patients with other chronic conditions $p<0.001$ (Wachtel et al., 1992).

Descriptive Measures

General Health History Form—This form gathers information about subjects' general health history, medical conditions, procedures, interventions, current review of symptoms, prescription medications, over-the-counter medications, supplements, vitamins and herbs. It also asks specific questions about DSP symptoms, diagnosis process, and management strategies.

Symptom Checklist—This is a brief assessment of sentinel symptoms associated with HIV disease progression. It also enables us to monitor any side effects of Acu/Moxa treatment. Symptom presentation that changes during the course of treatment will be attributed to the respective study group. Symptoms rated as severe will also be recorded as adverse events. The Symptom Checklist is administered at each study session.

Acupuncturist's Form—Acupuncturists record tongue and pulse assessments and TCM diagnosis at every session. Diagnostic questions and inquiry into symptom severity are purposefully not included in order to avoid treatment bias.

Credibility Assessment—This is a patient-rated instrument adapted from an acupuncture credibility assessment scale (Borkovec & Nau, 1972). It rates confidence that the Acu/Moxa treatment received is true and not placebo, confidence in the logic of treatment, success of treatment in alleviating DPS symptoms, confidence that symptom improvement is from the study treatments, likelihood of the study treatment to decrease symptoms in other conditions and whether they would recommend this treatment to a friend (Borkovec & Nau, 1972; Vincent, 1989). Scores range from 'very confident' (1) to 'not at all confident' (6).

Mini-Mental State Instrument—This is a short measure to assess an individual's mental state (Folstein et al., 1975) since the intervention and assessment require frequent sessions, instruction, completion of measures, subject's full attention and memory recall. The researcher asks the subject a series of short questions addressing their orientation, registration, attention, recall, language and level of consciousness.

Demographic Information Questionnaire—This questionnaire includes age, educational background, occupation and number of adults and children who live with the subject. Information is used to assess social factors that may influence health promotion behaviours, as suggested by public health epidemiology literature.

Discussion

Strengths

Understanding the intricacies of the clinical practice of acupuncture and moxibustion, in terms of assessment, diagnosis and administration of treatment, allowed our team to accomplish the challenging task of designing a trial that is both consistent with clinical practice and scientifically rigorous. This study is the first to combine acupuncture and moxibustion as one mode of therapy for reduction of pain and associated symptoms of HIV-related DSP. Traditionally, these modalities are used together to augment treatment. Rarely are they used in conjunction in studies testing TCM therapy. We developed the treatment protocol based on TCM diagnosis and treatment principles for the pattern differentiation of DSP in HIV. Locations of experimental acu-points and control sham points are described and diagrammed in a detailed manner in our procedure manual.

Consistent with the state of the science in acupuncture trials, this study protocol has been designed according to CONSORT and STRICTA guidelines and with methodology and design as the primary foci. All aspects of the protocol are detailed and formulated for consistency and reproducibility. To ensure protocol fidelity across treating acupuncturists, a study facilitator served as a monitor, observing and recording the protocol point locations, sequencing and timing. Neurological assessments give an additional, non-participant reported, measure of symptom changes.

Generalisability

Subjects are recruited from multiple health clinics and HIV organizations throughout New York City's five boroughs. The demographics of our participants are consistent with the demographics of the HIV/AIDS population in the New York City area, with the exception that participants who describe themselves as multiracial chose the 'Other' category for race (CDC, 2007).

Limitations

While the study did incorporate a protocol that factored in TCM diagnostic groupings to determine an appropriate point protocol, this study did not allow for the acupuncturists to formulate a treatment plan (individual point prescription, in this case) based on their assessments. All protocols were predetermined and did not allow for individualisation or customisation of treatment. A future, larger scale trial could incorporate a third arm that tests the efficacy of an individualised treatment arm that accommodates for individual variation, diagnostic pattern and symptom severity.

Conclusion

Patients with HIV-related DSP often experience feelings of isolation, frustration and despair due to the lack of a definitive diagnosis or adequate relief from their distressing symptoms. The goal for the care of individuals with HIV should include the relief of distressing symptoms, the promotion of optimal physical health and the improvement of quality of life. Quality of life can improve with the alleviation of physical and psychological distress, and maintenance of physical and mental functioning (Ferrell, Wisdom, Wenzl, 1989; Morris, Suissa, Sherwood, Wright, Greer, 1986).

Effective, non-invasive interventions are needed to help individuals with HIV manage these debilitating symptoms. Acu/Moxa is subtle as an intervention, holistic in approach and promising as a therapy that complements allopathic treatments for HIV. This study has been designed to assess the value of Acu/Moxa as an adjunctive therapy in the management of DSP in patients with HIV. By illustrating the rationale and components of this study, we hope to provide a useful reference for how a clinical trial is conducted.

Since the introduction of CONSORT, general standards of acupuncture trials have significantly improved (Prady, Richmond, Morton, MacPherson, 2008) and as time elapses, the more recent STRICTA guidelines will become further integrated. As acupuncture research advances, more well-designed trials will address the challenges and expand the understanding between Eastern and Western biomedicine.

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TABLE 1

STRICTA Guidelines (Intervention and description)

1 Intervention

1a) Style of acupuncture: Traditional Chinese Medicine; Chinese Acupuncture

1b) Rationale for treatment (e.g. syndrome patterns): expert panel review of protocol; grouping of TCM diagnoses, syndrome analyses and preliminary studies. TCM diagnoses: liver *qi* stagnation, liver *yin* deficiency, liver blood deficiency, spleen *qi* deficiency, spleen *yang* deficiency, kidney *qi* deficiency, kidney *yin* deficiency, kidney *yang* deficiency, *qi* & blood deficiency, *qi* & blood stagnation, dampness. Based on the grouping of TCM diagnoses and expert counsel we arrived at a specific set of acupuncture points for needling and moxa administration.

2 Needling details

2a) Needle type (gauge, length, and manufacturer or material):

All acupuncture procedures were performed with sterile disposable needles Seirin, J-type, 30 mm, 38 gauge.

Acupuncture points: LI 11, SP 10, GB 34, ST 36, SP 6, KI 3, LV 8, GB 39.

3 Treatment regimen

3a) Number of treatment sessions: Subjects received a total of 12 treatments.

3b) Frequency of treatment: Twice-weekly sessions for 6 weeks

4 Co-interventions

4a) Other interventions (e.g. moxibustion, cupping):

Moxibustion: All moxibustion procedures were performed with moxa sticks made of *Artemisia Vulgaris*

Active moxibustion – moxa stick was held approximately one inch over points.

Indirect pole moxa on UB 17, UB 18, UB 20, KI 1. Additional details in manuscript.

5 Practitioner background

5a) Practitioner background:

Research Acupuncturists: Criteria for serving as a Research Acupuncturist

- completed training from an accredited acupuncture programme which has received certification from the Accreditation Commission for Acupuncture and Oriental Medicine
- State Acupuncture license
- current certification from the National Commission for the Certification of Acupuncture and Oriental Medicine (which includes 'Clean Needle Technique' certification)
- have a minimum of two years experience
- have experience in serving as a Research Acupuncturist (following the research treatment protocol precisely as instructed).

In addition, prior to the implementation of the RCT all Research Acupuncturists:

- attended an acupuncture point location training session conducted by Research Acupuncture Consultant and PI
- pass a written and practical exam on point locations * (both traditional [true] and sham points)
- Research Acupuncturist and subject interaction – There was no discussion between the Research Acupuncturist and the subject. This was to maintain a research milieu and to ensure consistency and uniformity of protocol application.

All questions and/or comments were directed to the Study Facilitator (SF) who was present during all treatment sessions. Subjects were informed of this procedure at the time of consent. The SF role was otherwise scripted so that all subjects receive the same level of interaction.

- receive detailed instructions regarding the implementation of acupuncture procedures/techniques for all conditions from acupuncture consultant and PI
- reviewed current standards of practice including cleansing the site and proper disposal of needles.

Study Facilitator (SF) (Monitor Protocol Fidelity): The SF underwent training by an acupuncture consultant and the PI. SF training emphasis involved subject safety, methodical facilitation of all conditions, monitoring of protocols, timing and

sequencing of points, structured elicitation of adverse events, recording/documenting sessions, blinding procedures, unblinding subjects at final session and scheduling of post-study control subjects for active Acu/Moxa sessions.

5b) **Length of clinical experience:** Acupuncturists completed a 3 year, full-time (2,835 hours) programme, at a Council of Colleges of Acupuncture and Oriental Medicine (CCAOM) accredited institution. Acupuncturists were nationally certified by NCCAOM and New York State licensed.

5c) **Expertise in specific condition:** Study team has extensive experience in HIV-related conditions and symptom management.

6 Control intervention(s)

6a) **Intended effect of control intervention and its appropriateness to research question and, if appropriate, blinding of participants** (e.g. active comparison, minimally active penetrating or non-penetrating sham, inert):

Control interventions, sham acupuncture and placebo moxibustion, were designed specifically for two purposes:

1. to minimize the non-physiological effects (Birch et al., 2002), and 2) to maintain the psychological impact.

Sham acupuncture:

- **a.** void of treatment effect by specifying the exact anatomical location of sham points at 2–3 cm away from the classic/ traditional true point location and not on the channel/meridian
- **b.** minimally stimulating by ensuring an insertion depth of only 2 mm, which was just sufficient to make the needle stand vertically with very light [minimal] stimulation
- **c.** specifically void of manipulation of the needle so that no *qi* would be elicited
- **d.** applied a, b, and c (above) to sham acupuncture points.

Placebo moxibustion:

- **a.** void of treatment effect by specifying the exact anatomical location of control moxa 8 inches above and 2–3 cm away from the traditional location
- **b.** subjects were exposed to the moxibustion procedure by the lighting and administration of a moxa stick which emits smoke and a floral aroma, as in the true moxibustion
- **c.** specifically void of stimulation from the moxa stick so that no heat would be generated
- **d.** applied a, b, and c (above) to Placebo moxa points.

As an added measure to ensure blinding, all subjects were blindfolded during their treatments.

6b) **Explanations given to patients of treatment and control interventions:** All potential subjects are informed during consent procedures that: all subjects are randomised to either Active (true) Acu/Moxa or Sham/Placebo Acu/Moxa which is not an active treatment (non-treatment); all subjects are blinded treatment assignment and blind-folded during their treatments and that those subjects who were assigned to Sham/Placebo Acu/Moxa are offered 12 true Acu/Moxa treatments at no cost.

6c) **Details of control intervention** (precise description, as for Item 2 above): Details for control condition are as specific as the active treatment condition. All sham points are illustrated in our study procedure manual. All acupuncturists receive training and are tested on these points as well as the active points (written and practical exam).

6d) **Sources that justify choice of control:** (Birch et al., 2002; Hammerschlag, 1997; Stux & Hammerschlag, 2001, MacPherson et al., 2002; Vincent & Lewith, 1995; Vincent, 1989)

* classic text on Chinese medicine (Beijing College of TCM, 1987)

TABLE 2

Inclusion and Exclusion Study Criteria

Inclusion Criteria

- Men and women 18 years or older
- Diagnosed with HIV
- Pain associated with HIV-related DSP of the lower extremities (legs and feet) for 2 months or greater
- Experiencing ‘moderate’ pain based on the Gracely pain scale documented in a 1-week prospective self-report symptom diary
- Verification from primary care provider of subject’s: HIV status, diagnosis of DSP, and provider’s agreement that subject is clinically suitable for the study[(a)]
- Obtain a score of 24 or better on the mini-mental status examination
- Stable regimen (same drug(s), dose & frequency) of antiretroviral medications for 8 weeks or more prior to study entry[(b)]
- Stable regimen (same drug(s), dose & frequency) of analgesic medications and/or other medications which may have neuropathy listed as a side effect for a minimum of 21 days prior to study entry[(c)]
- Ability to understand and agree to complete daily symptom diaries for the duration of the study.

Exclusion Criteria

- Acute medical conditions or opportunistic infections (i.e. pneumocystis carinii pneumonia) which would require medical attention
- Diagnosis of diabetes mellitus, vitamin B-12 deficiency, coagulopathies
- History of severe cardiovascular disease, uncontrolled blood pressure, pulmonary disease, renal failure
- Pregnant women[(d)]
- Current alcohol or substance abuse
- Using topically applied medications to the lower extremities
- Current use of corticosteroids [rationale: steroids can decrease neuropathy signs and symptoms]
- Treated with INH, dapsone or metronidazole within 8 weeks prior to study enrollment
- Receiving acupuncture within 6 months of study enrollment
- History of using moxibustion
- Receiving other types of complementary therapies such as herbs, massage, reiki etc.
- Plans for travel, lifestyle change, or other activity that would preclude attending all of the study sessions and/or recording daily symptom diary information

*(a)*The statement of suitability is specific to the IRB requirements of our academic health science campus. All investigators are required to contact the patient’s physician and/or primary care provider to ensure that the provider is in agreement that their patient is clinically suitable for the clinical study in which the patient is planning to join.

*(b)*Many antiretroviral agents are associated with increased side effects during the initial weeks of treatment and generally subside after 4–6 weeks of use. To minimise the chance that reduction in symptom severity may be attributable to cessation of antiretroviral therapy side effects, we will require that all subjects are on a stable regimen for a minimum of 8 weeks prior to study enrolment.

*(c)*Since the study is 15 weeks in duration, it is anticipated that subjects will likely experience neuropathy symptoms. A criterion that totally denies the use of medications to reduce symptoms would be unethical and unrealistic, as well as potentially resulting in nonadherence to the study protocol. We will make note of any medications and handle this statistically.

*(d)*Prior to study entry, all women are required to take a urine HCG test to rule out pregnancy and to record menses (date, duration and heaviness of flow) during the study. Safety data for acupuncture in pregnancy are not available.