Protocol: Managing pain in people living with HIV/AIDS

Background:

With the introduction of ART, persons living with HIV/AIDS (PLWHA) have near normal life expectancy [1] but the quality of years gained may be severely compromised if PLWHA continue to suffer symptoms such as pain. While the HIV/AIDS pandemic initially required health care to focus on preventing mortality, the introduction of effective antiretrovirals has resulted in a shift to chronic disease management with an emphasis on enhancing quality of life.

Pain is among the commonest symptoms in PLWHA. It occurs at multiple sites and is typically of moderate to severe intensity [2]. The degree and quality of pain has been found to relate to psychosocial and demographic factors (e.g. perceived social support, female gender and depression [3, 4]) rather than biological markers of disease (e.g. viral load, CD4+ count or disease stage [5-7]). Pain is poorly managed in all PLWHA populations surveyed, [8, 9] including in South Africa [10, 11]. Reasons why pain management is challenging in the setting of HIV include difficulty using analgesic medications with antiretrovirals because of drug-drug interactions (highlighting the importance of non-pharmacologic methods), failure of some common HIV-associated pains, such as HIV neuropathy pain, to respond to available analgesics [12] (again, highlighting why non-drug measures may be important), the impediments posed by cost and/or availability of potent analgesics for typical patients attending busy HIV clinics in South Africa, and a paucity of high quality research into optimal non-pharmacological interventions for pain in PLWHA. This lack of response to pharmacological treatments highlights how essential a paradigm shift is towards non-pharmacological interventions for pain in HIV.

Exercise is a non-pharmacological intervention that has repeatedly been shown to benefit PLWHA, including improving self-efficacy [13-16] and reducing pain. A peer-led exercise and education intervention was developed and tested in a pilot study in South African amaXhosa women in Cape Town living with HIV/AIDS and pain [17]. Substantial reductions in pain occurred with the intervention, but some reduction also occurred in controls, who received the same education and assessments without the peer-led group exercise intervention. This raises the important question (to be addressed here) of whether the added expense of an exercise program is necessary. It may be that a therapeutic relationship (alone or with education) is a more cost effective, non-pharmacological intervention for pain in PLWHA in South Africa.

There is evidence that pain in HIV may be attenuated if the patient believes someone cares [18, 19]. With an estimated 5.6 million PLWHA in South Africa [20] and a reported pain prevalence of over 54% [2], there are probably over 3 million PLWHA living with pain in this country. It is thus critical to understand the precise additional benefit of any intervention over and above a caring therapeutic relationship alone, as this has real resource implications in our setting. Therefore, we are proposing different levels of intervention in the current protocol:

- A therapeutic relationship group who will return to the same research assistant (chosen for their warm and empathetic manner) for all follow up appointments;

- A therapeutic relationship, education and exercise group, who will additionally receive the relatively resource-intensive peer-led group exercise and goal setting intervention.

Sociodemographic factors (e.g. education, socioeconomic status and sex) may influence responses to pain-relieving interventions [21]. We will therefore assess both rural and urban populations. We will assess isiZulu speakers in a Johannesburg clinic and a rural Kwa-Zulu Natal hospital, rural amaXhosa speakers at a rural Eastern Cape hospital and urban Afrikaans speakers at an urban Cape Town clinic, thus controlling for language and culture.

Aims:

1. To measure the relative effects on pain and health-related quality of life in people with pain and HIV of:
    - a therapeutic relationship, without additional intervention
    - a therapeutic relationship together with education and a peer-led group exercise intervention

2. To explore responses to the interventions among urban isiZulu, rural isiZulu, rural isiXhosa and urban Afrikaans speakers with HIV.

Research Design and Methods:

Pre-study logistics: The Virology Clinic at Charlotte Maxeke Academic Hospital, a primary health care centre at Manguzi Hospital in rural Kwa-Zulu Natal, a primary health care centre at Zithulele Hospital in the Eastern Cape and a community health centre in Retreat, Cape Town (all with appropriate exercise or gym space) are the identified project sites. Project site coordinators are healthcare professionals enrolled in research-based higher degrees. Human Ethics approval have been obtained from the University of the Witwatersrand (Johannesburg site) and the Faculty of Health Sciences Research Ethics Committee of the University of Cape Town (remaining sites).

Educational material for the interventions utilise a Positive Living Workbook developed from freely available English language resources, translated and adapted for use in isiXhosa[17] and now isiZulu and Afrikaans. Workbooks accommodate low literacy levels and will be printed in English, isiZulu, isiXhosa and Afrikaans. Feedback from amaXhosa women [17] indicated patients prefer reading in English as well as their home language to improve comprehension.

Peer-leaders will be identified through community support networks (e.g. the Treatment Action Campaign; TAC). A male and a female peer-leader will be chosen for each site. Peer-leaders must be literate to Grade 10 level. They will be trained for the intervention over 3 weeks, for 3 hours 3 times each week.

Research assistants at each site will perform study related participant assessments. These are the individuals with whom the “therapeutic relationship” will be established. They will speak isiZulu/isiXhosa/Afrikaans (depending on site) and English, have matriculated high school, have vocational training in counselling and social care and will be chosen for their warm and empathetic

manner via community networks. Research assistants will complete the Good Clinical Practice course to train them in research methods and skills.

Methodology

A multi-centre randomized controlled trial is proposed. Patients attending the study sites for routine HIV care will be approached by the research assistant and screened for study eligibility (pain >3 months, stable HIV therapy for 6 months, isiZulu/isiXhosa/Afrikaans as home language). Eligible PLWHA will be invited to participate in a study exploring the benefits of exercise and education for adults with HIV. It will be made clear they have an equal chance of random assignment to each of the study arms. Consenting patients will be screened for exercise suitability using ACSM Guidelines by site coordinators prior to randomisation. Any patient unfit to exercise will not proceed further. To allow for 10 participants to be randomised to the exercise intervention before the group starts, we will recruit 50% of the cohort first. From previous experience we estimate this will take around 4 weeks. All participants will then be called in for baseline measures and randomisation.

Baseline measures will be obtained by the research assistant, then randomisation will occur on a 1:1 ratio using a computer generated random number sequence. Participants will receive R50 to cover transport costs for each subsequent study visit. Participants will be provided with an appointment card and will be contacted by short messenger service (SMS) with appointment reminders.

Recruitment will begin in March 2016. We expect (based on our previous HIV studies) to recruit 60 participants at each site within 6 months.

Sample size: With 20 participants in each group at each site, and allowing for up to 15% attrition rate, this study will have 90% power to detect an improvement in pain of 3 points on a numeric rating scale of 0-10 (a clinically significant change [22]) at six months in the exercise group versus 1 point in the therapeutic relationship only group, assuming an average baseline pain score of 6 (as seen in our previous study[17]) and a standard deviation of 1.8 (alpha=0.05).

Although some loss to follow up has been factored into our study design, we will maximize retention through phone contact and SMS reminders before study visits. If a participant is unable to attend a visit, questionnaires will be completed by phone.

Description of groups: Participants in the therapeutic relationship group will be assessed at baseline, 4, 8, 12, 24 and 48 weeks. They will see the same research assistant (chosen for their warm, empathetic manner) for each assessment. There will be time at the start for culturally-appropriate conversation (i.e. regarding the participant's family) before measures are completed.

Participants in the therapeutic relationship, education, and peer-led group exercise and goal setting intervention group will be provided with the Positive Living workbooks but will additionally attend the research site for a weekly group intervention for 6 weeks. They will undergo the same follow up measures at the same intervals as the other group and will again be assessed on each occasion by the same research assistant, including time for conversation.

When participants arrive for follow up visits, they will be greeted by the site coordinator, given an opportunity to ask questions and reminded NOT to disclose their group allocation to the research assistant.

Group exercise and goal setting intervention

The intervention was developed and tested in a trial in urban amaXhosa women [17] and will occur weekly for 6 weeks. Two-hour sessions will include education, discussion, exercise and facilitated relaxation. Exercise will initially consist of a 20-minute circuit including 2 minute intervals of aerobic, strengthening and stretching exercises. Exercise duration will increase by 2 minutes each week to 30 minutes. The exercises do not require specialist equipment and are designed for easy use at home. There will be one group for males and one for females, facilitated by peer leaders of the same sex. This is to respect cultural practices and encourage open discussion of sensitive issues including health and sex. Education and discussion will be based around information in the workbooks. Topics include: Week 1 Successful self-management and exercise; Week 2 Managing common symptoms of HIV/AIDS; Week 3 Stress management; Week 4 Pain; Week 5 Eating well and Week 6 Continuing as a successful self-manager. Each week's discussion includes a goal setting exercise where participants set goals for the week. Participants share goals with the group. A 10-15 minute facilitated relaxation led by the peer-leader concludes each session.

Outcome measures

Measures will be completed at baseline, 4, 8, 12, 24, 48 weeks

- The primary outcome measure will be pain severity measured on the Brief Pain Inventory on a numeric rating scale of 0-10 at 6 months compared with baseline values. The Brief Pain Inventory is validated for use in South African English, isiZulu and isiXhosa and the Afrikaans version will be validated in this study [23, 24]. The BPI will provide pain prevalence rates, measures of pain severity and pain interference with function.
- Depression will be measured using the validated Beck Depression Inventory [25] recommended by the IMMPACT group [22].
- Health-related quality of life will be assessed with the Euroquol-5D (EQ-5D) [26] (validated in a South African population, used in HIV cohorts and available in isiZulu[27, 28]).
- Self-efficacy will be measured using the chronic disease 6-item self-efficacy scale [29], validated in an HIV population [30].
- Physical function will be measured using the Simmonds battery of physical tests [31], validated in an HIV population[32].

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