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Corresponding Author: Mr. Kennedy Nkhoma, MSc

Corresponding Author's Institution: University of Nottingham

First Author: Kennedy Nkhoma, MSc

Order of Authors: Kennedy Nkhoma, MSc; Jane Seymour, PhD; Antony Arthur, PhD

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An Educational Intervention to Reduce Pain and Improve Pain Management for Malawian People Living with HIV/AIDS and Their Family Carers: A Randomized Controlled Trial

Kennedy Nkhoma, MSc, Jane Seymour, PhD, and Antony Arthur, PhD

Sue Ryder Care Centre for the Study of Supportive, Palliative and End of Life Care (K.N., J.S.), Division of Nursing, Queen's Medical Centre, Nottingham; and School of Nursing Sciences (A.A.), University of East Anglia, Norwich, United Kingdom

Address correspondence to:

Jane Seymour, PhD

Sue Ryder Care Centre for the Study of Supportive, Palliative and End of Life Care

Division of Nursing

Queen's Medical Centre

Nottingham, UK NG7 2UH

E-mail: jane.seymour@nottingham.ac.uk

Abstract

Context. Advances being made in improving access to HIV drugs in resource poor countries mean HIV patients are living longer, and, therefore, experiencing pain over a longer period of time. There is a need to provide effective interventions for alleviating and managing pain.

Objectives. To assess whether a pain educational intervention compared to usual care reduces pain severity and improves pain management in patients with HIV/AIDS and their family carers.

Methods. This was a randomized, parallel group, superiority trial conducted at HIV and palliative care clinics of two public hospitals in Malawi. One hundred eighty-two adults with HIV/AIDS (stage III or IV) and their family carers participated; carer participants were those individuals most involved in the patient's unpaid care. The educational intervention comprised a 30-minute face-to-face meeting, a leaflet and a follow-up telephone call at two weeks. The content of the educational intervention covered definition, causes and characteristics of pain in HIV/AIDS, beliefs and myths about pain and pain medication, assessment of pain, and pharmacological and non-pharmacological management. The primary outcome was average pain severity measured by the Brief Pain Inventory-Pain Severity. Assessments were recorded at baseline before randomization and at eight weeks after randomization.

Results. Of the 182 patient/carer dyads randomly allocated, 157 patient/carer dyads completed the trial. Patients in the intervention group experienced a greater decrease in pain severity (mean difference 21.09, points, 95% confidence interval 16.56, 25.63; P <0.001).

Conclusion. A short pain education intervention is effective in reducing pain and improving pain management for Malawian people living with HIV/AIDS and their family carers.

Trial registration: Current Controlled Trials ISRCTN72861423.

Key Words: HIV/AIDS, trial, pain, carers, educational intervention, palliative care

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Introduction

Advanced HIV infection and its treatment with antiretroviral therapy are associated with physical and psychological symptoms [1, 2]. These require focused assessment and management using locally available resources and interventions to optimize quality of life for patients and their carers [3, 4]. The negative impact of pain on quality of life has been documented in many studies [5, 6]. Pain is a major problem for people living with HIV/AIDS [7-9]. Pain is the most frequent and main cause of psychological distress [10, 11]. Experiencing pain can reduce adherence to drug regimens and quality of life for HIV/AIDS patients [12-16].

It is estimated that 35.3 million people were living with HIV/AIDS at the end of 2012 [17, 18]. In the same year, there were 1.6 million deaths from AIDS, a reduction from 2.3 million deaths in 2005. In 2010, 1.4 million people began HIV medication, an increase in the number of people receiving treatment from the previous year of 27%. Greater access to effective treatment largely explains some of this decline in HIV/AIDS mortality [19].

Sub-Saharan Africa has 10% of the world's population, but it is home to 69% of all people living with HIV/AIDS, making it the worst affected region [17, 18]. Antiretroviral therapy can dramatically increase survival and years of healthy life, but is unavailable in many parts of the region [19]. In 2010 in sub-Saharan Africa, the number of individuals treated with antiretroviral medication increased from 37% in 2009 [20] to 49% of the population eligible for treatment [21].

In Malawi the prevalence of HIV/AIDS is estimated at 11% of the population aged 15 to 49 years, with around 910,000 people living with HIV/AIDS at the end of 2011 [18]. Approximately 250 people are newly infected each day [21], and at least 70% of Malawi's hospital beds are occupied by HIV/AIDS patients [22], making Malawi the twelfth worst

affected country with HIV/AIDS worldwide [23]. However, there was a decline in HIV/AIDS prevalence from 14% in 2003 to 10% in 2011 predominantly because of increased access to antiretroviral therapy and preventive strategies [24]. Substantial progress has been made in the provision of HIV medication [25]. The involvement of nurses in the prescription and administration of medications and training health assistants to provide HIV counseling services has resulted in a greater proportion of patients starting HIV treatment within three weeks of diagnosis [26]. This has resulted in increased antiretroviral coverage to 67% in 2011 [24, 25].

Adequate pain control remains a challenge for HIV/AIDS patients and has an impact on their quality of life [14, 15]. Pain is experienced throughout the disease trajectory, severity being associated with later World Health Organization (WHO) clinical stage [2, 27-29], with an estimated 80% of people with advanced HIV infection experiencing severe pain [30]. Pain is also experienced as an effect of HIV medication [31, 32]. With advances being made in improving access to HIV drugs in resource poor countries, HIV patients are living longer, and, therefore, experiencing pain over a longer period [33, 34]. There is a need to provide effective interventions to HIV/AIDS patients in alleviating and managing pain. A systematic review [35] reported that self-management education programs for people living with HIV/AIDS results in short-term improvements in physical and psychosocial health and knowledge. However, all the trials reviewed were conducted in the U.S. and China where the health context is very different and none of these trials directly involved unpaid carers, a group likely to play a key role in the management of pain of those they care for.

Methods

Study Design

The pain education intervention study was a two-center, randomized, parallel group, wait-list controlled superiority trial. A detailed study protocol has been published [36].

Setting and Participants

From October 2012 to June 2013, we recruited participants at HIV and palliative care clinics within two public hospitals (Ekwendeni and Mzuzu Central) in northern Malawi. Both hospitals provide inpatient, clinic-based and home-based care for people with HIV/AIDS that includes active treatment and palliative care. Participants were people living with HIV/AIDS who had a primary carer who was identified as the individual most involved in their care. They were adults aged 18 years or over. All participants were able to read and write in English or Tumbuka (the vernacular language used in the northern part of Malawi). Participants were at WHO clinical stages III or IV of HIV/AIDS, or with a CD4 cell count of less than 350 cells, when the presence of pain and other symptoms is more likely because of opportunistic infections or side effects of HIV treatment. We excluded people living with HIV/AIDS if they had health problems that hindered cognition and communication such as HIV-associated dementia.

Recruitment

People living with HIV/AIDS in Malawi typically visit the hospital (palliative care clinics and HIV clinics) with their family members. Posters about the study entitled "Pain Education Study" were prominently displayed in the clinics. Additionally, the first author (K.N.) or staff in these clinics informed patients about the study and provided them with information sheets. Potential participants were encouraged to discuss the study with family members before making a decision to take part. Those interested in taking part in the study were asked by K.N. to provide written informed consent. A checklist was used to confirm that all criteria for study eligibility were met.

Randomization, Concealment of Allocation and Blinding

Baseline assessments were conducted by K.N. prior to randomization. Randomisation was implemented by K.N. using opaque, sealed and numbered envelopes. The envelope was opened in the presence of the participant. Participants had a 50% chance of being allocated to either the pain education intervention group or usual care group. In order to limit imbalance between the treatment groups, participants were randomly assigned with block randomization using the "ralloc" command in Stata v. 12 [37]. This allocates participants at random in blocks of sizes 2, 4, 6, 8 and 10, with block sizes allocated unequally in the ratio of 1:4:6:4:1 (Pascal's triangle).

Randomization was stratified by recruiting hospital. K.N. was not involved in the preparation of envelopes and was blinded to block size. A.A. prepared the envelopes and had no contact with the study participants, nor was he involved in recruitment. Owing to the nature of the intervention, participants and K.N. knew the treatment arm to which they were allocated, but the nurses who conducted follow-up outcomes were blinded to this information. Participants were told not to inform the assessors about treatment allocation. Assessors were asked if participants had told them of their group allocation after completion of outcome assessments to assess the success or failure of blinding.

Intervention and Comparator Groups

Pain Education Intervention. The nurse-led pain education intervention was informed by a biopsychosocial approach [38] to the management of pain among people with HIV/AIDS. It was designed to provide a systematic and proactive approach to assist people with HIV/AIDS and their carers to better understand and manage pain. The intervention consisted of a health education session delivered face-to-face by K.N., a Malawian registered nurse and specialist in

palliative care, to the individual patient-carer dyads (Table 1). The face-to-face session took approximately 30 minutes in a quiet room within the palliative care or HIV/AIDS clinic where the participant was recruited. The components of the pain education intervention are listed in detail elsewhere [36] but included a discussion of HIV/AIDS-related pain, beliefs and myths about pain and pain medication, ways to assess pain, and potential pharmacological and non-pharmacological methods to manage pain. A leaflet entitled "All About Your Pain" was given to participants, who were given the opportunity to look through it (Appendix, available at jpsmjournal.com). K.N. then discussed the contents of the leaflet with the participants and they were both encouraged to ask questions. Participants received a phone call reminder from K.N. after two weeks to inquire whether they had any further questions after the face-to-face discussion and reading the leaflet. Phone contacts typically lasted no more than five minutes. In order to minimize possible contamination between two groups, participants were asked not to share the leaflet with others. The features of usual care and the pain education intervention are explained in Table 1. There was no intention to systematically manage pain differently between the two groups but one consequence for those in the pain education intervention group may have been to seek out additional treatments to manage their pain.

The leaflet drew on the evidence base and related literature for cancer pain management [39, 40] and HIV/AIDS pain management in Africa [41, 42] and pain management in Malawi [43]. Health care workers, HIV/AIDS patients and family carers were involved in the development of the leaflet in terms of its design, content, technical characteristics, and readability.

The leaflet was in the form of a double-sided A4 page formatted so that it could be gate-folded into two for ease of use. It was printed in color and had Illustrations to improve clarity

and understanding. Diagrams and pictures were used to enhance understanding and to motivate the reader. The leaflet was pilot-tested among 10 patients and 10 family carers to ensure that the content was readable and understandable.

Usual Care. Information relating to pain management is typically provided in a responsive rather than proactive manner and ad hoc rather than systematic, with the focus restricted to pharmacological treatment of pain. Pain assessments are not usually conducted in a systematic way and not recorded routinely. It is unusual for this information to be routinely shared with patients and/or their carers.

Outcomes

The primary outcome was average pain severity measured using the Brief Pain Inventory (BPI-PS) [44]. Secondary outcomes were pain interference with daily activities measured using the mean score of the seven pain interference items of the Brief Pain Inventory (BPI-PI) [45], knowledge of pain management measured using the knowledge subscale of the Patient Pain Questionnaire PPQ-K [46], and quality of life measured using the APCA African Palliative care Outcomes Scale (POS) [47, 48]. For carers, knowledge of pain management was measured using the knowledge subscale of the Family Pain Questionnaire (FPQ-K) [49], carer motivation was measured using the Picot Caregiver Rewards Scale (PCRS) [50], and quality of life was measured using the APCA African POS [47]. All outcomes were self-reported. If participants were unable to self-complete after careful and standardized explanation of individual items, they were asked the question verbally and interviewers recorded their responses. While the BPI [51] and APCA African POS [52] have both been used previously in Sub-Saharan African populations, use of the PPQ, FPQ and PCRS has been restricted to populations in Western countries. Our experience immediately prior to trial recruitment of piloting these scales as part of

the questionnaire among 10 patients and 10 carers suggests that they are acceptable to and understood by members of the population of patients and carers from which our sample was recruited.

All outcome measures were conducted at baseline and eight weeks after delivery of the intervention. Eight weeks was considered sufficient time to observe any effect of the intervention and long enough to be considered clinically important. Outcomes were transposed to a 0 to 100 scale, with higher scores indicating a more "positive' outcome"; hence, a participant's individual score represented a percentage of the best possible score for that outcome.

Sample Size

We wished to be able to detect a mean difference of 10% between the treatment groups in the primary outcome measure (average pain severity on the BPI). A 10% improvement is the difference considered the lower limit of changes considered clinical important [53]. Using a *P*-value cut-off of 0.05 to determine a statistically significant result, 76 people per arm of the trial were needed to complete the study to give 80% power to detect such a difference. This is based on a review [54] that suggests that education-based interventions are able to produce this level of improvement in pain reduction, and that a standard deviation of 2.2 points is a liberal estimate of variability. To allow for 15% attrition, we aimed to recruit 182 participants to the trial.

Statistical Analysis

All patients and carers were analyzed according to the group to which they were randomized, although the use of strict intention-to-treat analysis is only possible where there is no loss to follow-up [55, 56]. We compared treatment groups in terms of our primary outcome measure (average pain severity using the BPI-PS treated as a continuous measure) using a linear regression model, with baseline BPI and treatment group and recruitment center as covariates.

Analysis of each of the six secondary outcomes (BPI-PI, PPQ-K, APCA African POS patient score, FPQ-K, PCRS, APCA African POS carer score) were conducted using six equivalent models, with estimates of treatment effect conditional on the value of the outcome at baseline. Sensitivity analysis was performed as follows: we conducted secondary analyses that 1) adjusted for variables that were considered potential predictors of outcome (age, gender, number of pain medications at baseline) assuming missing at random, and 2) considered plausible scenarios for departures from the missing at random assumption using the Stata command "rctmiss" [56]. These scenarios were for all outcomes using scores of the mean outcome plus and minus 20 points for both arms and individual arms. All models included recruitment center as a covariate. All analyses were conducted using Stata version 12 [37].

Ethical Approval

The study was approved by the University of Nottingham Medical School Research Ethics Committee (SNMP 11042012) and the National Health Sciences Research Committee of Malawi (NHSRC 1023).

Results

Of the 308 potential patient/carer dyads assessed, 182 were eligible, consented to participate and completed baseline measures (Fig. 1). Ninety-two were randomized to the pain education intervention and 90 were randomized to usual care. Of these, 15 patient/carer dyads and 10 carers were lost to follow-up. Reasons for attrition in the pain education group were patient having died before follow-up assessments (n=4), no transport (n=2), untraceable (n=1) and moved away (n=1). Reasons for attrition in the usual care group were: untraceable (n=2), moved away (n=4) and patient too unwell (n=1). Reasons for carer loss to follow-up in the pain education group and usual care group were the same: carer too busy (n=2) and no transport

(*n*=3). Of the 167 patients and 157 carers who completed the trial, complete data were available for all outcomes.

Baseline Characteristics

Pain education and usual care groups were similar at baseline in terms of sociodemographic profile except for gender; there were 43 (46.7%) male patients in the pain education group compared with 56 (62.2%) male patients in the usual care group (Table 2). There were also differences in carer relationship to the patient; there were 35 (38.0%) spousal carers in the pain education group and 44 (48.9%) spousal carers in the usual care group. At baseline, the two groups of patient/carer dyads were broadly similar in terms of the seven outcome measures.

Delivery and Receipt of the Intervention

The intervention was delivered by K.N. All the participants (*n*=92) randomized to the pain education intervention attended a 30-minute face-to-face discussion and received a leaflet. Of these, 59 participants received the phone call reminder intervention at week two. Because of poor telephone network coverage, some participants did not receive a phone call (*n*=19) but had physical contact with K.N. during their visit to the clinic at week two. Of the 59 participants who received a phone call, four also had face-to-face contact with K.N. at the clinic, where they were reminded to read the leaflet and clarification was provided in response to their questions.

Primary Outcome

Both groups had reduced average pain severity at follow-up. However, those in the pain education group had a mean change of 40.95 (SD 23.78) while the usual care group had a mean change of 19.27(SD 25.27) (Table 3). When adjustments were made for baseline average pain severity score, recruitment center, age, gender and number of pain medications, participants in

the pain education group reported less severity of pain compared to those in the usual care group (mean difference 21.25, 95% confidence interval [CI] 16.7, 25.8; *P* <0.001).

Secondary Outcomes

Participants in the pain education group had significantly less pain interference than the usual care group at follow-up (adjusted mean difference 24.5, 95% CI 19.61, 29.38; *P*<0.001). Patients in the pain education group reported greater improvement in knowledge than patients in the usual care group at follow-up (adjusted mean difference 20.39, 95% CI 17.51, 23.27; *P*<0.001). At follow-up, participants in the pain education group experienced better quality of life than participants in the usual care group (adjusted mean difference 28.76, 95% CI 24.62, 32.91; *P*<0.001) (Table 3).

Carers in the pain education group reported greater improvement in knowledge than carers in the usual care group at follow-up (adjusted mean difference 20.32, 95% CI 17.37, 23.28; *P*<0.001) (Table 4). Carers in the pain education group reported greater motivation to provide care than carers in the usual care group at follow-up (adjusted mean difference 7.64, 95% CI 5.15, 10.13; *P*<0.001), as well as a better quality of life (adjusted mean difference 34.16, 95% CI 30.15, 38.17; *P*<0.001).

Sensitivity Analysis

In all the scenarios tested using various departures from the missing at random assumption, none altered the interpretation of better outcomes for the pain education group.

Discussion

In this randomized controlled trial, we found evidence that pain education intervention consisting of a face-to-face discussion, leaflet and two-week follow-up phone call reduced pain severity, reduced pain interference with daily activities, improved patient knowledge of pain

management and patient quality of life. We also found evidence that the intervention improved carers' pain knowledge of pain management, quality of life, and motivation to provide care. The results are consistent with other studies of interventions to enhance self-care that have found improvement in pain management [57, 58], better knowledge about pain [59-61], improved pain control [58, 59, 62, 63] and less pain interference with daily activities [62, 63] although the form, content and context of these interventions were different and were administered among cancer patients. Our findings are different from those of a study conducted among HIV/AIDS patients [64] that found decreased quality of life when medication reminders were given, and to a trial that found no effect of an educational intervention to enhance self-management skills [65]. Our finding of improved knowledge about pain among people with HIV/AIDS is consistent with a large trial [66] that found significant improvement in knowledge among HIV/ AIDS participants following an HIV medication adherence intervention. The effect of the intervention on family carers is also consistent with other studies among family carers of people with cancer [67] and dementia [68]. Previous studies of family carers also found that family members feel rewarded and more prepared in their caregiving role if education is provided to them [69, 70].

Strengths and Limitations

To our knowledge, this is the first randomized controlled trial to be conducted in sub-Saharan Africa to recruit patient and carer dyads. The dearth of research into HIV/AIDS-related pain in African populations means that, for some outcomes, we have had to infer validity from validation studies conducted outside of Africa. The sample size of 182 was larger than other trials of pain education interventions, which have, hitherto, been conducted in Western countries and targeting cancer patients [57, 58, 62] or cancer patients and their carers [60, 63]. Recruitment to our trial was successful and attrition relatively low at 15% loss to follow-up. The main reasons

for loss to follow-up were death of the patient, patient transferred to another center, lack of transport, and carer being too busy.

This was a complex intervention and the nature of the intervention meant that it was not possible to blind participants of group allocation; we cannot exclude the possibility that patients and carers in the pain education intervention group may have responded more positively as a result of getting greater attention. However, social desirability bias is likely to have been limited by the use of staff nurses, blinded to allocation, conducting outcomes although we cannot be sure that participants did not divulge that information.

The follow-up measures were conducted eight weeks after randomisation; this was sufficient time to observe the effects of the intervention and is consistent with other pain education studies [71, 72]. However, we do not know whether the positive results we observed are likely to be sustained beyond that time frame. Pain education participants were asked not to report the face-to face discussion and not to pass the leaflet to any staff member or other patients to minimize contamination between two groups. However the possibility of contamination cannot be excluded because participants lived in the same community where we had no means to prevent them from sharing the leaflet. Clustering the participants and randomizing according to some natural grouping such as area or clinic could have avoided contamination thereby reducing type II error [73], but the scale of such a study would have required resources exceeding those available to us.

Conclusion

The current practice in HIV/AIDS and palliative care clinics in much of sub-Saharan Africa does not prioritize the provision of health-related information among patients. This study, conducted in Malawi, has provided strong evidence that a simple pain education intervention

comprising a leaflet and verbal advice can reduce pain severity and interference, and improve pain knowledge and quality of life outcomes among HIV/AIDS patients. To build on these important findings, future research should include a health economic analysis. This would establish whether the benefits observed for patients and carers are accompanied by benefits to the wider health economy.

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References

1. Kell ME, Walley JD. Palliative care for HIV in the era of antiretroviral therapy availability: perspectives of nurses in Lesotho. BMC Palliat Care 2009;8:11.
2. Tapsfield JB, Bates MJ. Hospital based palliative care in sub-Saharan Africa; a six month review from Malawi. BMC Palliat Care 2011;10: 12.
3. Wantland DJ, Holzemer WL, Moezzi S, http://www.ncbi.nlm.nih.gov/pubmed/?term=Willard%20SS%5BAuthor%5D&cauthor=true&cauthor_uid=18400461et al. A randomized controlled trial testing the efficacy of an HIV/AIDS symptom management manual. J Pain Symptom Manage 2008; 36:235-246.
4. Kell ME, Walley JD. Palliative care for HIV in the era of antiretroviral therapy availability: perspectives of nurses in Lesotho. BMC Palliat Care 2009;8:11.

5. Wahab KW, Salami AK. Pain as a symptom in patients living with HIV/AIDS seen at the outpatient clinic of a Nigerian tertiary hospital. J Int Assoc Physicians AIDS Care (Chic) 2011;10:35-39.

6. Oldham L, Kristjanson LJ. Development of a pain management programme for family carers of advanced cancer patients. Int J Palliat Nurs 2004;10:91-99.

7. Newshan G, Sherman DW. Palliative care: pain and symptom management in persons with HIV/AIDS. Nurs Clin North Am 1999;34:131-145.

8. Newshan G., Pain in human immunodeficiency virus disease. Semin Oncol Nurs 1997; 13:36-41.

9. Harding R, Powell RA, Kiyange F, Downing J, Mwangi-Powell F. Provision of pain- and symptom-relieving drugs for HIV/AIDS in sub-Saharan Africa. J Pain Symptom Manage 2010;40:405-415.

10. Vogl, D., et al., Symptom prevalence, characteristics, and distress in AIDS outpatients. J Pain Symptom Manage, 1999. 18(4): p. 253-62.

11. Marcus KS, Kerns RD, Rosenfeld B, Breitbart W. HIV/AIDS-related pain as a chronic pain condition: implications of a biopsychosocial model for comprehensive assessment and effective management. Pain Med 2000;1:260-273.

12. Hughes J, Jelsma J, Maclean E, Darder M, Tinise X. The health-related quality of life of people living with HIV/AIDS. Disabil Rehabil 2004;26:371-376.

13. Hughes A., Symptom management in HIV-infected patients. J Assoc Nurses AIDS Care 2004;15(5 Suppl):7S-13S.

14. Hudson A, Kirksey K, Holzemer W. The influence of symptoms on quality of life among HIV-infected women. West J Nurs Res 2004;26:9-23; discussion 24-30.

15. Brechtl JR, Breitbart W, Galietta M, Krivo S, Rosenfeld B. The use of highly active antiretroviral therapy (HAART) in patients with advanced HIV infection: impact on medical, palliative care, and quality of life outcomes. J Pain Symptom Manage 2001; 21: 41-51.

16. Holzemer WL, Hudson A, Kirksey KM, Hamilton MJ, Bakken S. The revised Sign and Symptom Check-List for HIV (SSC-HIVrev). J Assoc Nurses AIDS Care 2001;12: 60-70.

17. UNAIDS. UNAIDS report on the global AIDS epidemic 2013. 2013. Available from: http://www.unaids.org/en/resources/campaigns/globalreport2013/factsheet/.

18. World Health Organization. HIV Global update on HIV treatment: Results, impact and opportunities. Geneva: World Health Organization, 2013. Available from: http://apps.who.int/iris/bitstream/10665/85326/1/9789241505734_eng.pdf

19. UNAIDS, UNAIDS report on the global AIDS epidemic. 2010. AU: PROVIDE URL

20. Callaghan M, Ford N, Schneider H. A systematic review of task-shift ing for HIV treatment and care in Africa. Hum Resour Health 2010;8:8.

21. WHO/UNAIDS/UNICEF, Global HIV/AIDS response: Epidemic update and health sector progress towards Universal Access 2011. AU: PROVIDE URL

22. Kumwenda JJ, Mateyu G, Kampondeni S, et al. Differential diagnosis of stroke in a setting of high HIV prevalence in Blantyre, Malawi. Malawi Med J 2005;17: 107-111.

23. Lawson M, Messenger S, Nkhoma-Mbawa F, Noel T. Malawi Essential Health Services Campaign. Oxfam International Research Report. Oxford: Oxfam International, 2008.

24. Malawi Government. Global AIDS response progress report: Malawi country: report for 2010 and 2011. 2012. AU: PROVIDE URL

25. UNAIDS, Global Report: UNAIDS Report on the Global AIDS Epidemic 2012. 2012. AU: PROVIDE URL

26. World Health Organisation. Global HIV/AIDS response – Epidemic update and health sector progress towards Universal Access – Progress report. Geneva: World Health Organization, 2011.

27. Grant L, Brown J, Leng M, Bettega N, Murray SA. Palliative care making a difference in rural Uganda, Kenya and Malawi: three rapid evaluation field studies. BMC Palliat Care 2011; 10:8.

28. Namisango E, Harding R, Atuhaire L, et al., Pain among ambulatory HIV/AIDS patients: multicenter study of prevalence, intensity, associated factors, and effect. J Pain 2012; 13: 704-713.

29. Selwyn P. Why should we care about palliative care for AIDS in the era of antiretroviral therapy? Sex Transm Infect 2005;81:2-3.

30. Solano JP, Gomes B, Higginson IJ. A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. J Pain Symptom Manage 2006;31:58-69.

31. Peltzer K, Preez NF, Ramlagan S, Fomundam H. Use of traditional complementary and alternative medicine for HIV patients in KwaZulu-Natal, South Africa. BMC Public Health 2008;8:255.

32. Heath KV, Montaner JS, Bondy G, et al., Emerging drug toxicities of highly active antiretroviral therapy for human immunodeficiency virus (HIV) infection. Curr Drug Targets 2003;4:13-22.

33. Harding R, Higginson IJ. Palliative care in sub-Saharan Africa. Lancet 2005;365:1971-1977.

34. Harding R, Karus D, Easterbrook P, et al. Does palliative care improve outcomes for patients with HIV/AIDS? A systematic review of the evidence. Sex Transm Infect 2005;81:5-14.

35. Millard T, Elliott J, Girdler S. Self-management education programs for people living with HIV/AIDS: a systematic review. AIDS Patient Care STDS 2013;27:103-113.

36. Nkhoma K, Seymour J, Arthur A. An educational intervention to reduce pain and improve pain management for Malawian people living with HIV/AIDS and their family carers: study protocol for a randomised controlled trial. Trials 2013;14:216.

37. StataCorp LP. Stata statistical software: release 12. College Station, TX: StataCorp LP, 2011.

38. Engel GL. The need for a new medical model: a challenge for biomedicine. Science 1977;196:129-136.

39. Scottish Intercollegiate Guidelines Network (SIGN). Cancer pain: Booklet for patients and carers. Edinburgh: SIGN Executive 2009:2-29.

40. Oldham L, Kristjanson LJ. Development of a pain management programme for family carers of advanced cancer patients. Int J Palliat Nurs 2004;10:91-99.

41. African Palliative Care Association (APCA). A palliative care training manual: community based casegicers in Africa. Kampala: APCA, 2008:156-159.

42. African Palliative Care Association (APCA). Beating pain: A pocketguide for pain management in Africa. Kampala: APCA, 2012:7-78.

43. Ministry of Health, Introduction to palliative care: Health professionals training manual., Lilongwe, Malawi: Ministry of Health, 2008;41-50.

44. Keller S, Bann CM, Dodd SL, et al. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. Clin J Pain 2004;20:309-318.

45. Dworkin RH, Turk DC, Farrar JT, et al., Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;113:9-19.

46. Ferrell BR, Ferrell BA, Ahn C, Tran K. Pain management for elderly patients with cancer at home. Cancer 1994;74(7 Suppl):2139-2146.

47. Harding R, Selman L, Agupio G, et al., Validation of a core outcome measure for palliative care in Africa: the APCA African Palliative Outcome Scale. Health Qual Life Outcomes, 2010;8:10.

48. Powell RA, Downing J, Harding R, Mwangi-Powell F, Connor S; APCA. Development of the APCA African Palliative Outcome Scale. J Pain Symptom Manage 2007;33:229-232.

49. Ferrell BR, Rhiner M, Rivera M. Development and evaluation of the Family Pain Questionnaire. J Psychosocial Oncol 1993;10:21-35.

50. Picot SJ, Youngblut J, Zeller R. Development and testing of a measure of perceived caregiver rewards in adults. J Nurs Meas 1997;5:33-52.

51. Beck SL, Falkson G. Prevalence and management of cancer pain in South Africa. Pain 2001;94:75-84.

52. Harding R, Selman L, Agupio G, et al. Validation of a core outcome measure for palliative care in Africa: the APCA African Palliative Outcome Scale. Health Qual Life Outcomes 2010;8:10.

53. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9: 105-121.

54. Bennett MI, Bagnall AM, Jose Closs S. How effective are patient-based educational interventions in the management of cancer pain? Systematic review and meta-analysis. Pain 2009;143:192-199.

55. Abraha I, Montedori A. Modified intention to treat reporting in randomised controlled trials: systematic review. BMJ 2010;340:c2697.

56. White IR, Horton NJ, Carpenter J, Pocock SJ. Strategy for intention to treat analysis in randomised trials with missing outcome data. BMJ 2011;342:d40.

57. Miaskowski C[1], Dodd M, West C, et al., Randomized clinical trial of the effectiveness of a self-care intervention to improve cancer pain management. J Clin Oncol 2004;22:1713-1720.

58. Yildirim YK, Cicek F, Uyar M. Effects of pain education program on pain intensity, pain treatment satisfaction, and barriers in Turkish cancer patients. Pain Manag Nurs 2009; 10: 220-228.

59. de Wit R, van Dam F, Zandbelt L, et al., A pain education program for chronic cancer pain patients: follow-up results from a randomized controlled trial. Pain 1997;73:55-69.

60. Wells N, Hepworth JT, Murphy BA, Wujcik D, Johnson R. Improving cancer pain management through patient and family education. J Pain Symptom Manage 2003;25:344-356.

61. Yates P, Edwards H, Nash R, et al., A randomized controlled trial of a nurse-administered educational intervention for improving cancer pain management in ambulatory settings. Patient Educ Couns 2004;53:227-237.

62. Oldenmenger WH, Sillevis Smitt PA, van Montfort CA, de Raaf PJ, van der Rijt CC. A combined pain consultation and pain education program decreases average and current pain and decreases interference in daily life by pain in oncology outpatients: a randomized controlled trial. Pain 2011;152:2632-2639.

63. Lin CC, Chou PL, Wu SL, Chang YC, Lai YL. Long-term effectiveness of a patient and family pain education program on overcoming barriers to management of cancer pain. Pain 2006;122:271-281.

64. Wu AW, Snyder CF, Huang IC, et al. A randomized trial of the impact of a programmable medication reminder device on quality of life in patients with AIDS. AIDS Patient Care STDS 2006;20:773-781.

65. Gifford AL, Laurent DD, Gonzales VM, Chesney MA, Lorig KR. Pilot randomized trial of education to improve self-management skills of men with symptomatic HIV/AIDS. J Acquir Immune Defic Syndr Hum Retrovirol 1998;18:136-144.

66. Goujard C, Bernard N, Sohier N, et al. Impact of a patient education program on adherence to HIV medication: a randomized clinical trial. J Acquir Immune Defic Syndr 2003;34:191-194.

67. Hudson P, Thomas T, Quinn K, Cockayne M, Braithwaite M. Teaching family carers about home based palliative care: final results from a group education program. J Pain Symptom Manage 2009;38:299 - 308.

68. Graff MJ, Vernooij-Dassen MJ, Thijssen M, et al., Community based occupational therapy for patients with dementia and their care givers: randomised controlled trial. BMJ 2006; 333: 1196.

69. Henriksson A, Årestedt K, Benzein E, Ternestedt BM, Andershed B. Effects of a support group programme for patients with life-threatening illness during ongoing palliative care. Palliat Med 2013;27:257-264.

70. Northouse LL[1], Katapodi MC, Song L, Zhang L, Mood DW. Interventions with family caregivers of cancer patients: meta-analysis of randomized trials. CA: Cancer J Clin 2010;60:317-339.

71. Clotfelter CE. The effect of an educational intervention on decreasing pain intensity in elderly people with cancer. Oncol Nurs Forum 1999;26:27-33.

72. Hudson P, Aranda S, Hayman-White K. A psycho-educational intervention for family caregivers of patients receiving palliative care: a randomised controlled trial. J Pain Symptom Manage 2005;30:329 - 341.

73. Torgerson DJ. Contamination in trials: is cluster randomisation the answer? BMJ 2001; 322:355.

Table 1. Features of Usual Care and the Pain Educational Intervention

Element	**Usual Care/Wait-List Control**	**Pain Education Intervention**
General description	Unstructured verbal information	Leaflet-based information, advice, explanation and discussion
Form	General information on the treatment prescribed and instructions to be followed, responsive information from staff nurses	Information leaflet distributed "All About Your Pain" including 30-minute face-to-face verbal instructions and advice on pain assessment and management, phone call reminder after two weeks
Content	General information about HIV/AIDS medication and treatment compliance	Specific information about procedure on pain assessment and classification using pain scales and pain diagrams, including pain management using WHO analgesic ladder and specific drugs on each step
Written materials	None	Leaflet with simplified text information and diagrams, pictures/photos for quick reference
Method of delivery	General staff members	K.N.

Table 2. Baseline Characteristics of Participants (*N*=182) Randomized to the Pain Education Intervention or Usual Care

Variables	**Pain Education Intervention (*n*=92)**	**Usual Care (*n*=90)**
Patient participants		
Mean (SD) age in yrs	40.5 (11.3)	41.3 (11.65)
Gender		
Male	43 (46.74)	56 (62.22)
Female	49 (53.26)	34 (37.78)
Marital status		
Married	61 (66.3)	58 (64.44)
Single	11 (11.96)	13 (14.44)
Divorced/separated	11 (11.96)	10 (11.11)
Widow/widower	9 (9.78)	9 (10)
Education		
Primary school	21 (22.83)	14 (15.56)
High school	66 (71.74)	72 (80)
College/University	5 (5.43)	4 (4.44)
BPI pain measures, mean (SD)		
Average pain severity	50.76 (24.86)	51.22 (27.1)
Pain interference	49.91 (27.97)	49.46 (29.48)
Pain knowledge. Mean (SD)		
PPQ-K subscale	67.78 (16.61)	66.24 (18.84)
Quality of life mean (SD)		
APCA African POS subscale	44.78 (22.79)	48.92 (20.5)
Carer participants		
Mean (SD) age in yrs	41.1 (11.7)	42.6 (SD 11.4)
Gender		

Male	14 (15.56)	19 (21.11)
Female	76 (84.44)	71 (78.89)
Marital status		
Married	78 (84.78)	81 (90)
Single	10 (10.87)	6 (6.67)
Divorced/separated	1 (1.09)	1 (1.11)
Widow/widower	3 (3.26)	2 (2.22)
Education		
Primary	21 (22.8)	22 (24.4)
High school	66 (71.7)	64 (71.1)
College/University	5 (5.4)	4 (4.4)
Carer relationship to patient		
Spouse	35 (38.04)	44 (48.9)
Sibling	27 (29.4)	20 (22.2)
Son/daughter	10 (10.9)	4 (4.4)
Friend	0	2 (2.2)
Parent	12 (13)	14 (15.6)
Other	8 (8.7)	6 (6.7)
Pain knowledge, mean (SD)		
FPQ-K subscale	65.29 (16.93)	64.59 (18.53)
Motivation. mean (SD)		
PCRS	78.91 (11.29)	79.41 (11.02)
Quality of life mean (SD)		
APCA African POS subscale	44.2 (18.95)	45.26 (18.55)

Table 3. Patient Outcomes: Average Pain Severity on the BPI-PS for Pain Education and Usual Care Groups

Primary Outcome	**Pain Education (*n*=84)**	**Usual Care (*n*=83)**	**Adjusted for Baseline Average Pain Severity and Recruitment Center**		**Adjusted for Baseline Average Pain Severity, Recruitment Center, Age, Gender and Number of Pain Medications**	
			Mean Difference (95% CI)	***P*-value**	**Mean Difference (95% CI)**	***P*-value**
BPI-PS subscale						
Mean (SD) average pain severity score						
At baseline (*n*=182)	50.76 (24.86)	51.22 (27.1)				
At follow-up (*n*=167)	92.62 (8.23)	71.69 (21.18)				
Mean change (SD) from baseline	40.95 (23.78)	19.27 (25.27)	21.09 (16.56, 25.63)	<0.001	21.25 (16.7, 25.8)	<0.001
Secondary Outcomes	**Pain Education (*n*=84)**	**Usual Care (*n*=83)**	**Adjusted for Baseline score and Recruitment Center**		**Adjusted for Baseline Score, Recruitment Center, Age, Gender and Number of Pain Medications**	
BPI-PI subscale						
Mean (SD) pain interference						
At baseline (*n*=182)	49.91 (27.97)	49.46 (29.48)				
At follow-up (*n*=167)	93.67 (9.33)	69.24 (25.21)				
Mean change (SD) from baseline	42.5 (25.91)	18.42 (23.92)	24.32 (19.33, 29.32)	<0.001	24.5 (19.61, 29.38)	<0.001
PPQ-K subscale						
Mean pain						

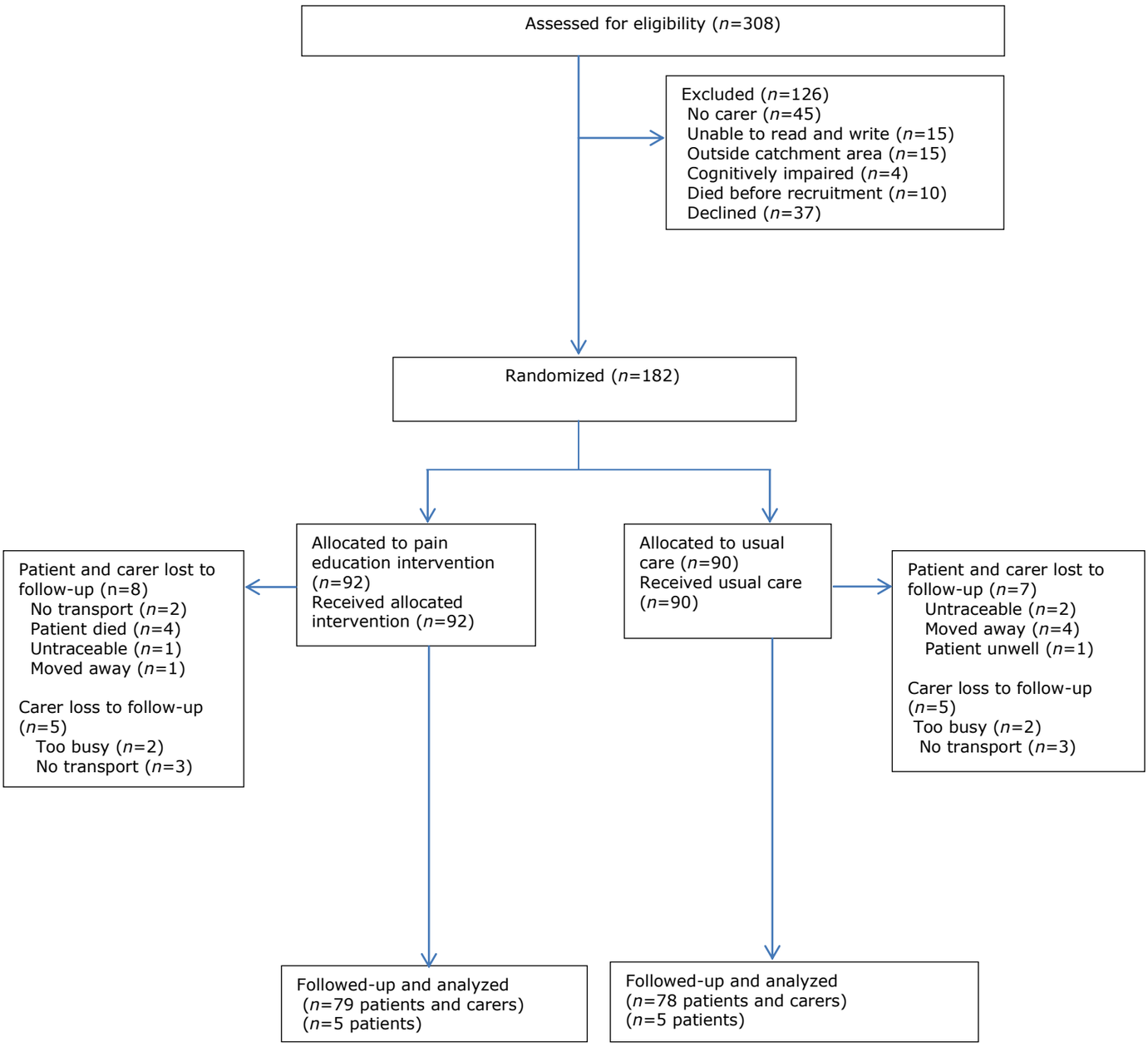
knowledge						
At baseline (*n*=182)	67.78 (16.61)	66.24 (18.84)				
At follow-up (*n*=167)	92.63 (8.16)	71.98 (15.21)				
Mean (SD) change from baseline	25.63 (15.5)	6.32 (11.00)	20.05 (17.25, 22.86)	<0.001	20.39 (17.51, 23.27)	<0.001
APCA African POS-patient subscale						
Mean (SD) POS						
At baseline (*n*=182)	44.78 (22.79)	48.92 (20.5)				
At follow-up (*n*=167)	90.58 (9.0)	63.37 (19.46)				
Mean (SD) change from baseline	45.44 (22.58)	14.46 (18.77)	28.32 (24.12, 32.53)	<0.001	28.76 (24.62, 32.91)	<0.001

Table 4. Carer Outcomes: Pain Knowledge, Motivation and Quality of Life for Carer Participants

Outcomes	**Pain Education (*n*=79)**	**Usual Care (*n*=78)**	**Adjusted for Baseline Score and Recruitment Center**		**Adjusted for Baseline Score, Recruitment Center, Age, Gender and Number of Pain Medications**	
			Mean Difference (95% CI)	***P*-value**	**Mean Difference (95% CI)**	***P*-value**
FPQ-K subscale						
Mean pain knowledge						
At baseline (*n*=182)	65.29 (16.93)	64.59 (18.53)				
At follow-up (*n*=157)	91.36 (7.8)	70.26 (15.88)				
Mean (SD) change from baseline	27 (15.8)	7.17 (9.8)	20.51 (17.58, 23.44)	<0.001	20.32 (17.37, 23.28)	<0.001
PCRS						
Mean (SD) motivation						
At baseline (*n*=182)	78.91 (11.29)	79.41 (11.02)				
At follow-up (*n*=157)	97.13 (5.87)	89.52 (11.14)				
Mean (SD) change from baseline	18.01 (11.96)	10.18 (8.48)	7.7 (5.26, 10.14)	<0.001	7.64 (5.15, 10.13)	<0.001
APCA African POScarer subscale						
Mean (SD) POS						
At baseline (*n*=182)	44.2 (18.95)	45.26 (18.55)				
At follow-up (*n*=157)	92.66 (8.84)	58.55 (17.94)				
Mean (SD) change from baseline	47.68 (18.86)	13.42 (16.63)	34.13 (30.16, 38.09)	<0.001	34.16 (30.15, 38.17)	<0.001

Figure(s)

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram of patients and carers throughout the study.



Figure(s)

ONLINE ONLY Appendix: Information leaflet "All about your pain"

'All about your pain'

Pain is one of the symptoms that are commonly experienced in HIV infection. HIV pain is experienced due to two main reasons:

1. Due to advanced HIV infection such as: headache, general body weakness, neck pain, chest pains, painful swallowing.

2. Due to side effect of HIV medication such as: abdominal pain, feeling of shooting, stabbing on your hands and feet's which sometimes makes you unable to walk or hold anything with your hands.

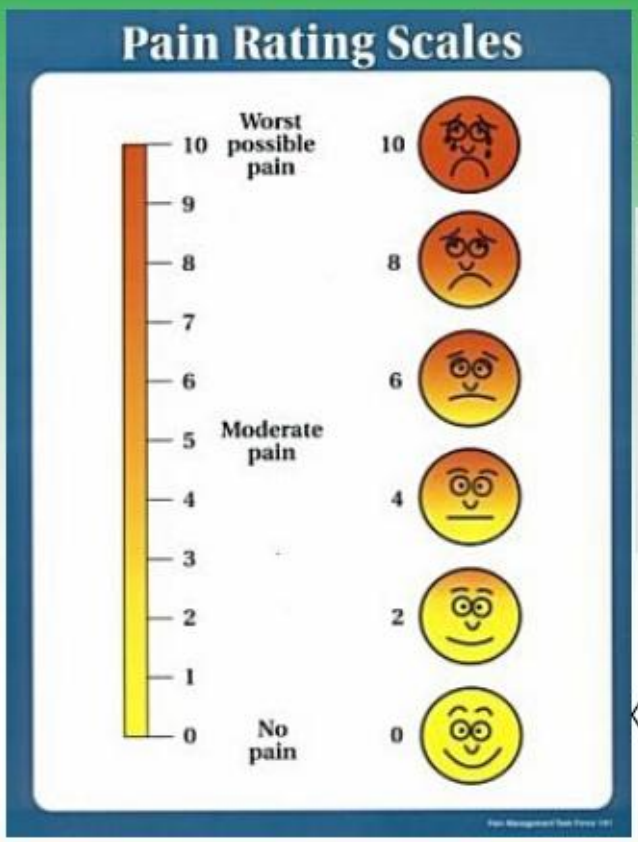
When you experience any form of pain , it is important to come to the hospital to be examined by the doctor.

Even though pain will always be experienced it can easily be managed even at home. This booklet will teach you how to assess pain and manage it at home.

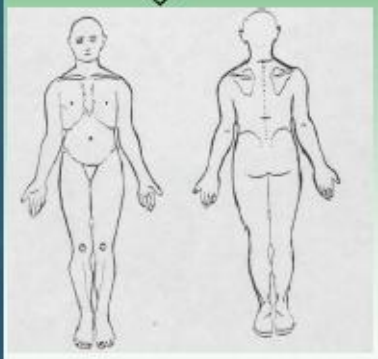
Pain Assessment

Using pain diagrams:

- You can locate your pain.
- Describe how you experience the pain like shooting, burning, pricking, itching.
- Describe what makes the pain worse and what relieves the pain.
- Use of tools to determine the intensity of pain.
- Using pain scales you can rate your pain by relating to the assessment tools.



Using pain diagrams you can locate your pain .



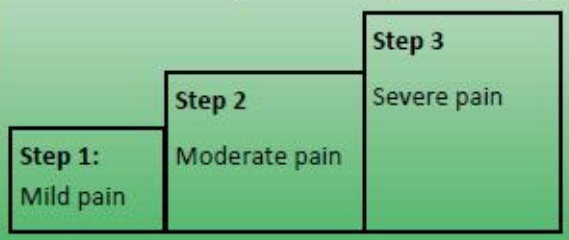
Using pain scales (0-10) you can rate your pain.

Using the faces you can classify your pain.

Pain Management

Pain is managed by using a ladder developed by World Health Organisation. After locating the pain and assessing the pain, classify it as mild, moderate or severe. The World Health Organisation management guides which treatment to use after classification of pain.

World Health Organisation pain management ladder



Step 1 is mild pain which ranges from 0-3 on the universal assessment scale on for this type of pain we use paracetamol (Panado) 2 tablets, 4 times in a day. You can also use Asprin 2 tablets, 4 times a day.

Step 2 is moderate pain which ranges from 4-6 on the universal assessment scale and for this type of pain we use Diclofenac 1 tablet, 4 times in a day or you may use codeine 1 tablet or 2 tablets, 4 times in a day.

Step 3 is severe pain which ranges from 7-10 on the universal scale. Here we use Morphine. It is either in tablet or solution form. If it is tablets form you take 2 tablets 6 times in a day if in solution form then 2 tea spoons 6 times in a day.

Make sure that you take the drugs at the required time, do not wait for the pain to come, and do not stop taking the drugs if you are not feeling pain, you need to take them all any time according to prescription because if you stop taking them, then the pain will come again.

Misconceptions about your pain and pain medication

Patients exaggerate the pain.

Patients need to experience the pain.

Patients should not continuously take pain medication because they will become addicted.

Good patients do not complain about their pain.

Important points to remember

Pain can be controlled and managed with drugs.

Patients have the right to complain about their pain.

Patients should talk to the doctor or nurse as soon as pain begins.

Patients have the right to pain control.

Patients should not let fear keep them in pain.

Patients have the right to appropriate assessment and management of pain.
All HIV/AIDS patients can live a pain free life.

Pain medication should be given using the following principles:

By the mouth Giving pain medication by mouth is the simplest and most reliable method for most patients. Dissolve the tablets in water if the patient has mouth sores for easy swallowing.

By the clock Constant pain needs regular pain medication to keep it away. Pain that is allowed to build up is more difficult to control. Do not wait for the pain to return but give pain medication at regular intervals according to their duration of action.

By the ladder The World Health Organisation pain management ladder gives a logical way of increasing the strength of pain medication in steps as pain increases.

Other ways of managing pain.

You also need to do the following when in pain to distract it apart from taking the drugs:

- Apply warm compress on the site where there is pain.
- Take warm fluids when feeling abdominal pains.
- Wash your mouth with salty water every day 4 times in a day if you have oral sores.
- Read a newspaper, magazine or this booklet if in pain or any reading material you find interesting like Bible, Quran.
- Play soft music or tell stories to the patient.
- Give gentle massage on the area where patient feels pain.
- Perform relaxation exercises like deep breathing regularly.
- Elevate feet's and legs if they are swollen.
- Seek pastoral support and prayer.

References

APCA (2008) A palliative care training manual: community based male caregivers in Africa

PACAM (2008) Palliative care A field guide for community home-based care volunteers

The Worldwide palliative care alliance (2008) Palliative care tool kit

WHO (2006) Caregiver booklet: symptom management and end of life care

Contact person: Kennedy Nkhoma on 0991696828/0888715056

Please quote ref no:

E-mail
ntxkn1@nottingham.ac.uk

Faculty of Medicine and Health Sciences
School of Health Sciences

B Floor
The Medical School
Queen's Medical Centre
Nottingham
NG7 2UH
Telephone 0115 8230491

23rd December 2014

Dear Editor

Revised Manuscript

Ms. Ref. No.: JPS-D-14-00616
Title: An educational intervention to reduce pain and improve pain management for Malawian people living with HIV/AIDS and their family carers: a randomised controlled trial (*ISRCTN72861423***)**

Thank you for giving us the opportunity to revise our manuscript in response to reviewers' comments. We are extremely pleased with the positive response by both reviewers. Reviewer 2 has made three suggestions and we are pleased to accommodate these in our revised manuscript. The changes made on the revised manuscript have been underlined.

Comment	**Action**
Further justification for the design (for example why not a cluster trial to avoid contamination?)	We have expanded our original point about the risk of contamination to discuss the potential benefits of a cluster randomised design. In the discussion section this has now been added: *Clustering the participants and randomising according to some natural grouping such as area or clinic could have avoided contamination thereby reducing type II error [73], but the scale of such a study would have required resources exceeding those available to us.*
Justification for the time 2 data collection point within the methods section rather than just in the discussion section	We have now added a sentence to the methods section to justify the timing of outcome measures: *Eight weeks was considered sufficient time to observe any effect of the intervention and long enough to be considered clinically important.*
Include detail in the discussion	The reviewer makes an important

about future research recommendations, e.g., to explore resource/health economic costs of the intervention, etc.	point and we now expand on our concluding paragraph accordingly: *To build on these important findings, future research should include a health economic analysis. This would establish whether the benefits observed for patients and carers are accompanied by benefits to the wider health economy.*

All authors have seen and approved the revised manuscript. Please contact me if you require any further information.

Thank you for your consideration. We look forward to hearing from you in due course.

Yours sincerely

Kennedy Nkhoma

***Response to Reviewers**

Thank you for giving us the opportunity to revise our manuscript in response to reviewers' comments. We are extremely pleased with the positive response by both reviewers. Reviewer 2 has made three suggestions and we are pleased to accommodate these in our revised manuscript. The changes made on the revised manuscript have been underlined.

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3,4
	2b	Specific objectives or hypotheses	2
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5,6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6,7,8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	6

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	6,7,8,21
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9,10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	10,22
	13b	For each group, losses and exclusions after randomisation, together with reasons	10, 22
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	23
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	24,25,26
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	24,25,26
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	24,25,26
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	13,14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	12,13,14
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	5
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	15

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Direct line/e-mail
+44 (0) 115 8231063
Louise.Sabir@nottingham.ac.uk

Faculty of Medicine and Health Sciences

Medical School Research Ethics Committee
Division of Therapeutics & Molecular Medicine
D Floor, South Block
Queen's Medical Centre
Nottingham
NG7 2UH

Tel: +44 (0) 115 8231063
Fax: +44 (0) 115 8231059

27th April 2012

Mr Kennedy Nkhoma
PhD Student
c/o Dr Anthony Arthur
Associate Professor
Room B58, Sue Ryder Care Centre
School of Nursing Midwifery & Physiotherapy
QMC Campus
Nottingham University Hospitals
NG7 2UH

Dear Mr Nkhoma

Ethics Reference No: SNMP11042012 PLWHA Kennedy
Study Title: An educational intervention to reduce pain and improve pain management for people living with HIV/AIDS and their family carers in Malawi: randomised controlled trial.
Student Lead Investigator: Mr Kennedy Nkhoma, PhD student, School of Nursing Midwifery & Physiotherapy.
Supervisor/Chief Investigator: Dr Anthony Arthur, Associate Professor, Professor Jane Seymour, Sue Ryder Care Professor, School of Nursing, Midwifery and Physiotherapy

Thank you for the above application dated 11th April 2012 and the following documents were received:

- Letter for ethics.docx 05 April 2012
- Application form.doc 05 April 2012
- Information Sheet for family carers.docx 11 April 2012
- Consent form for family carersdocx.docx 11 April 2012
- Carers administered questionnaire.docx 05 April 2012
- Pain Education Poster.pptx final.pdf 05 April 2012
- Protocol.docx 05 April 2012
- Consent form for PLWHA.docx 11 April 2012
- Information Sheet for PLWHA.docx 11 April 2012
- Questionnaire for PLWHA.docx 05 April 2012
- E-mail response to Ethics queries 18 April 2012
- Letter of support from Osborn N.I. Mwalwanda, Chief Clinical Officer, Cordinator, Wananangwa HIV/AIDs Clinic, Ekwendeni Hospital, Malawi dated 19th April 2012

These have been reviewed and are satisfactory and the study protocol is approved.

Approval is given on the understanding that the Conditions of Approval set out below are followed.

Ethics Committee approval is sought from the National Health Science Research Committee in Malawi. Please can you submit a copy of the approval letter when it is available.

Conditions of Approval

You must follow the protocol agreed and any changes to the protocol will require prior Ethics' Committee approval.

This study is approved for the period of active recruitment requested. The Committee also provides a further 5 year approval for any necessary work to be performed on the study which may arise in the process of publication and peer review.

You promptly inform the Chairman of the Research Ethics Committee of

(i) Deviations from or changes to the protocol which are made to eliminate immediate hazards to the research subjects.

(ii) Any changes that increase the risk to subjects and/or affect significantly the conduct of the research.

(iii) All adverse drug reactions that are both serious and unexpected.

(iv) New information that may affect adversely the safety of the subjects or the conduct of the study.

(v) The attached End of Project Progress Report is completed and returned when the study has finished.

Yours sincerely

Dr Clodagh Dugdale
Chair, Nottingham University Medical School Research Ethics Committee

Medical School Research Ethics Committee
Membership 2011/2012

Chair	Dr Clodagh Dugdale, University Teacher in Sports and Exercise Medicine, Division of Orthopaedic and Accident Surgery, School of Clinical Sciences.
School	**Representative**
Biomedical Sciences	Dr Vince Wilson, Reader and Basic Scientist. Dr Liz Simpson, Chief Experimental Officer.
Molecular Medical Sciences	Dr David Turner, Clinical Associate Professor in Microbiology.
Community Health Sciences	Dr Gill Doddy, Clinical Associate Professor & Reader in General Adult Psychiatry, Division of Psychiatry
Clinical Sciences	Dr Abdol Nateri, Lecturer, Pre-Clinical Cancer Studies Division of GI Surgery
Graduate Entry Medical School	Dr Caroline Chapman, Associate Professor, Breast Surgery.
Clinical Sciences Human Development	Professor Harish Vyas, Consultant & Special Professor in Paediatric Intensive Care Unit and Respiratory Medicine, Children's Respiratory Unit, E Floor, East Block, QMC Campus, Nottingham University Hospitals Trust.
Primary Care	Dr Richard Knox, General Practitioner/ Part-time Lecturer Division of Primary Care, QMC Campus
School of Nursing, Midwifery and Physiotherapy	Dr Jayne Brown, Senior Research Fellow University of Nottingham, Sue Ryder Care Centre
Lay (Out of Faculty)	Professor Nigel White, Professor of Public International Law, School of Law, University of Nottingham. Lydia Davies-Bright, PhD Student, School of Law. Dr Mary Stephenson, Research Fellow, SPMMRC, School of Physics and Astronomy.
Medical Students nominated by ISC	To be appointed, 3rd Year Medical Student
Postgraduate Student Member	Prema Nirgude PhD student, Division of Psychiatry Catrin Middleton, PhD student, Division of Breast Surgery
Administrator	Mrs Louise Sabir, Division of Therapeutics & MM, School of Clinical Sciences

Telephone: + 265 789 400
Facsimile: + 265 789 431
e-mail doccentre@malawi.net
All Communications should be addressed to:
The Secretary for Health and Population

In reply please quote No. MED/4/36c

MINISTRY OF HEALTH
P.O. BOX 30377
LILONGWE 3
MALAWI

18th June, 2012

Kenedy Nkhoma
University of Nottingham

Dear Sir/Madam,

RE: Protocol # 1023: An educational intervention to reduce pain and improve the management of pain among people living with HIV/AIDS and their family carers in Malawi: a randomized controlled trial

Thank you for the above titled proposal that you submitted to the National Health Sciences Research Committee (NHSRC) for review. Please be advised that the NHSRC has **reviewed** and **approved** your application to conduct the above titled study.

- **APPROVAL NUMBER : NHSRC # 1023**
  The above details should be used on all correspondence, consent forms and documents as appropriate.
- **APPROVAL DATE : 18/6/2012**
- **EXPIRATION DATE** :This approval expires **on 18/06/2013**
  After this date, this project may only continue upon renewal. For purposes of renewal, a progress report on a standard form obtainable from the NHSRC secretariat should be submitted one month before the expiration date for continuing review.
- **SERIOUS ADVERSE EVENT REPORTING** :All serious problems having to do with subject safety must be reported to the National Health Sciences Research Committee within 10 working days using standard forms obtainable from the NHSRC Secretariat.
- **MODIFICATIONS**: Prior NHSRC approval using standard forms obtainable from the NHSRC Secretariat is required before implementing any changes in the Protocol (including changes in the consent documents). You may not use any other consent documents besides those approved by the NHSRC.
- **TERMINATION OF STUDY**: On termination of a study, a report has to be submitted to the NHSRC using standard forms obtainable from the NHSRC Secretariat.
- **QUESTIONS**: Please contact the NHSRC on Telephone No. (01) 724418, 0999218630 or by e-mail on moh@gmail.com
- **Other:**
  Please be reminded to send in copies of your final research results for our records as well as for the Health Research Database.

Kind regards from the NHSRC Secretariat.

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FOR CHAIRMAN, NATIONAL HEALTH SCIENCES RESEARCH COMMITTEE