Can palliative care integrated within HIV outpatient settings improve pain and symptom control in a low-income country? A prospective, longitudinal, controlled intervention evaluation

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(Received 8 June 2012; final version received 28 September 2012)

A high burden of pain, symptoms and other multidimensional problems persist alongside HIV treatment. WHO policy indicates palliative care as essential throughout the disease course. This study aimed to determine whether palliative care delivered from within an existing HIV outpatient setting improves control of pain and symptoms compared to standard care. A prospective, longitudinal controlled design compared patient outcomes at an outpatient facility that introduced palliative care training to clinicians and stocked essential palliative care drugs, to outcomes of a cohort of patients at a similar HIV care facility with no palliative care, in Tanzania. Inclusion criteria were clinically significant pain or symptoms. Patients were followed from baseline fortnightly until week 10 using validated self-report outcome measures. For the primary pain outcome, the required sample size of 120 patients was recruited. Odds of reporting pain reduced significantly more at intervention site (OR = 0.60, 95% CI 0.50–0.72) than at control (OR = 0.85, 95% CI 0.80–0.90), p = 0.001. For secondary outcomes, longitudinal analysis revealed significant difference in slope between intervention and control, respectively: Medical Outcomes Study-HIV (MOS-HIV) physical score 1.46 vs. 0.54, p = 0.002; MOS-HIV mental health 1.13 vs. 0.26, p = 0.006; and POS total score 0.84 vs. 0.18, p = 0.001. Neither baseline CD4 nor antiretroviral therapy (ART) use was associated with outcome scores. These data are the first to report outcomes evaluating integrated HIV outpatient palliative care in the presence of ART. The data offer substantive evidence to underpin the existing WHO clinical guidance that states an essential role for palliative care alongside HIV treatment, regardless of prognosis.

Keywords: palliative; HIV; evaluation; pain; symptoms

Background

High prevalence of pain (Norval, 2004) and symptoms at all stages of HIV infection are reported in low-income settings, including fatigue (Voss et al., 2007), anorexia, weight loss, depression, agitation and anxiety, nausea and vomiting, diarrhoea, cough, dyspnoea, fever, sweats and pruritus (Simms, Higginson, & Harding, 2011; Wakeham et al., 2010). This emphasises the need for palliation alongside disease-oriented intervention from diagnosis. Multi-dimensional problems are prevalent from diagnosis (Simms et al., 2011) and go beyond the physical domain to include psychological (Kaharuza et al., 2006; Marwick & Kaaya, 2010), social and existential/spiritual problems. Spiritual well-being constitutes the greatest contribution to self-reported quality of life among patients with HIV and/or cancer in sub-Saharan Africa (Selman et al., 2011). High prevalence and burden of physical symptoms (Harding et al., 2005; Harding, Lampe, et al., 2010; Harding, Molloy, Easterbrook, Frame, & Higginson, 2006; Mathews et al., 2000) and psychological distress (Sherr et al., 2008) have also been demonstrated in high-income settings with universal antiretroviral therapy (ART) access. A significant proportion of patients on ART experience problems such as peripheral neuropathy and gastrointestinal problems (Heath et al., 2003). These treatment effects may require drug discontinuation or treatment change within, and between, ART classes (Dieleman et al., 2002). Further, there is some evidence that symptom burden is associated with suboptimal adherence (Harding, Lampe, et al., 2010) and sexual risk taking (Harding et al., 2012; Harding, Lampe, et al., 2010).

The World Health Organization (WHO) states palliative care (i.e., assessment and control of the physical, psychological, spiritual and social problems in potentially life-limiting disease) to be an essential component of HIV clinical management from diagnosis until death should it come (WHO, 2006).

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UNAIDS stipulates provision of palliative care to improve quality of life for all HIV patients, and that it is not only indicated at the end of life (UNAIDS, 2000). However, evidence suggests inadequate clinical attention to pain and symptom assessment and control in HIV management (Justice, Chang, Rabeneck, & Zackin, 2001), and patients perceive that their symptoms remain untreated (Harding & Molloy, 2008). This lack of attention to palliative care-related problems since the advent of ART has led to suboptimal care and support of persistent, highly prevalent and burdensome problems (Simms, Higginson, & Harding, 2012).

In a systematic review, HIV palliative care has been shown to be effective in the management of pain, symptoms and anxiety (Harding et al., 2005), although the identified data were almost exclusively generated in high-income settings prior to the advent of ART. A dearth of sub-Saharan African evidence has been identified (Harding & Higginson, 2005), although an East African study identified around half of HIV outpatients to be appropriate for palliative care intervention irrespective of the ART use (Collins & Harding, 2007). Despite a growing body of evidence for high prevalence and associated burden of multidimensional problems throughout the HIV trajectory, and policy and clinical guidance for delivery of palliative care within routine HIV management, there has been a lack of research activity to develop and test palliative care interventions in HIV disease. A recent study from Vietnam suggested that palliative care integrated into routine HIV outpatient care improved pain and symptom control, depression and perceived social support (Green et al., 2010).

This study aimed to evaluate, in terms of patient outcomes, palliative care delivered by the existing HIV outpatient clinical personnel in Tanzania, compared to standard HIV outpatient care.

Methods

Study design
This study used a prospective, longitudinal, controlled intervention evaluation, comparing outcomes for patients accessing care from an HIV outpatient facility that introduced palliative care training to its staff and stocked essential palliative care drugs to outcomes of a cohort of patients at a similar HIV care facility with no palliative care.

Setting and facilities
The study was conducted in Tanzania in 2009–2010. The two comparison sites were chosen as they had both been offering standard “Care and Treatment Centre” (CTC) for HIV patients for at least 36 months, have similar ART treatment and adherence preparation models, offer home-based care, and receive technical assistance for HIV care and treatment from the same implementing partner.

Intervention
The palliative care site (“intervention”) operates an outpatient and in-patient HIV service in the North East of Tanzania from a district hospital providing HIV care across 4922 km² with a population of 280,000, of which around 90% are rural. A multidisciplinary palliative care team was formed including the HIV medicine department, the hospital chaplain, the social worker and other allied hospital staff. Several members of the team underwent training to diploma level at Hospice Africa Uganda or Nairobi Hospice, and these subsequently delivered training to other staff at the intervention facility. Of the approximately 8000 patients enrolled in HIV care, almost 4500 were currently on ART. The novel aims of the integrated HIV palliative care service were to ensure that all the existing HIV clinical staff received training in palliative care, that essential drugs be available for control of common pain and symptoms, and that all patients be provided with holistic assessment and management emphasising multidimensional person-centred care. Training involved a minimum of one week, with an ongoing training programme for all staff. Training broadly focused on communication skills, holistic management of pain and other symptoms, and the assessment and control of psychological, social and spiritual needs. At the time of the study a Clinical Officer had gained a Diploma in Palliative Medicine, and clinical mentorship was provided in blocks throughout the year to all staff by experienced international palliative care practitioners. In order to ensure that pain is controlled in line with the WHO pain ladder (WHO, 2007) morphine has been acquired (oral morphine liquid in a strength of 1 mg/ml), and staff trained in pain relief in line with the pain ladder (i.e., from non- opioids to strong opioids with adjuvants as required). The supply of morphine from the local Cancer Institute was steady throughout the period except for a shortage experienced nationally for about 6 weeks. Other analgesics included paracetamol, Ibuprofen and Diclofenac and Tramadol. Other medications made available to facilitate control of prevalent symptoms include paracetamol, Non-steroidal anti-inflammatory drugs (NSAIDs) and Tramadol for pain, amitryptilline, carbamezipine and steroids as adjuvants, metoclopramide and haloperidol for...
nausea and vomiting, and vincristine for the treatment of Kaposi’s Sarcoma. In line with the definition of palliative care the team is multiprofessional and includes physicians, nurses, chaplain and a social worker. The facility’s village health worker network also received lay palliative care training.

**Control**

The comparison site with no staff trained in palliative care (“control”) is the regional hospital for a region in the North West of Tanzania. It serves as primary referral hospital for the region and provides inpatient and outpatient HIV care services to a population of almost 3,000,000, and covers in an area of 19,592 km². At the time of the study, the clinic actively provided HIV care to almost 8000 patients, of whom around 4000 were on ART. Morphine was not available in this hospital during the study, but tramadol, a WHO step two pain medication (i.e., weak opioid) and step one pain analgesics (i.e., non-opioids) were available. Other essential palliative care drugs were not available, e.g., metoclopramide and haloperidol, at the control site. Palliative care training was not provided to any control site staff.

The control site was selected as it offered similar standard care prior to palliative care initiation at the intervention site, care and support were organised similarly due to having the same implementing partner, there were no plans to introduce palliative care at the time of the study (and indeed none was until the final patient exited the study) and the geographical areas and facility organisation were similar. Apart from the palliative care intervention components, the two sites offer the same medications, laboratory facilities and procedures, and specialty back-up. They both serve a mainly rural population of around 300,000 people.

At both sites, the most common first line treatment at the time of the study was the triple therapy single table including 3TC, d4T and Nevirapine, but Efavirenz and azidothymidine (AZT) were also available. Second line treatment was Kaletra, didanosine and abacavir. Informal feedback suggests that physicians are reluctant to change to second line treatment, and that the inability to measure viral load and the not infrequent lack of reagents to measure CD4 mean that patients on ART can live with resistance undiagnosed.

**Recruitment and inclusion criteria**

The facility triage nurse at each site screened consecutive outpatients against study inclusion criteria as they attended clinics for routine usual outpatient care. Inclusion criteria were adult patients (aged at least 18 years) who knew their HIV diagnosis, presenting for outpatient HIV care, and able to give informed consent in a local language or English. Training for the research nurse at each site and manualised scripted recruitment procedures gave identical recruitment procedures in both sites.

The final inclusion criterion was that patients needed to self-report pain or symptoms. In order to measure potential participants against this criterion (on which the sample size was calculated), all consecutive patients were asked at triage whether they had any pain or other symptoms. Those who answered yes to this question were referred to the dedicated study researcher, who administered the pain and symptom items of the APCA African POS outcome tool (details below). Those who scored 3, 4 or 5 on the POS (i.e., those who self-reported the worst pain or symptom intensity responses on a scale of 0–5) were deemed to have met this final entry criterion and were given an information sheet (read-out to them) and asked for written consent to enter the study. The exclusion criterion was pain or symptoms related to an acute infection (e.g., malaria, urinary symptoms or vomiting/diarrhoea of less than seven days duration). Patients were recruited into the study after the intervention training site was complete, and the required drugs were in place. The pre-evaluation implementation of palliative care skills allowed the learning effect to be minimised, i.e., clinicians were able to deliver an optimal intervention through practice.

Ethical approval was granted by the University of Maryland School of Medicine Institutional Review Board in the USA and the National Institute for Medical Research in Tanzania.

**Data collection**

Following enrolment into the study, patients participated in six rounds of data collection, i.e., at baseline then every two weeks until week 10. Due to the additional costs of attending research interview over attendance at usual care, participants were paid US$3 for each completed data point. Any patient admitted to the wards during the study was followed up at their place of care. Study-specific researchers who were not responsible for any delivery of care collected the data, and each questionnaire was read aloud to patients in Swahili. Two Tanzanians fluent in the Tanzanian dialect of Swahili independently translated all information, consent forms and questionnaires.

**Measurement tools**

Demographic and disease-oriented variables were collected once at baseline (T0): patient age, gender,
most recent CD4, ART treatment status, WHO HIV staging and the number of children for whom the patient had responsibility.

The following tools were implemented at each point of data collection (i.e., T0–T5). The APCA African POS is an adapted version of the original Palliative Outcome Scale (POS), and was developed and validated in 10 centres in 8 sub-Saharan African countries (Harding, Selman, et al., 2010; Powell, Downing, Harding, Mwangi-Powell, & Connor, 2007). In line with the WHO definition of palliative care, the 10 items address the 3-day period prevalence of physical, psychological, emotional and spiritual problems of patients and families, and employ scoring methods appropriate for a range of literacy skills. The validation study demonstrated its properties included sensitivity to change, and it has high levels of patient and clinician acceptability.

The Medical Outcomes Study-HIV (MOS-HIV) is a widely used quality of life measure that has been culturally adapted to the African setting (Mast et al., 2004; Stewart, Hays, & Ware, 1988). The 35 items address the domains of role function; pain; physical functioning; cognitive functioning; overall health perception; mental health; and vitality. The weighted subscores in these domains combine to produce two summary scores measuring physical health and mental health (Revicki, Sorensen, & Wu, 1998).

All data were patient self-report (reflecting the importance of patient self-report outcome measures) (Dawson, Doll, Fitzpatrick, Jenkinson, & Carr, 2010) except CD4 count, WHO staging and ART status which were extracted from patient medical records.

Sample size calculation
The sample size calculation was conducted using an APCA African POS pain score 1.0 as a clinically meaningful difference, at a power of 80% and using a data-set of HIV outpatients with ART access from Kenya and Uganda (24) demonstrating a standard deviation of 1.67, at a significance level of 5% and an intra-cluster coefficient of 0.02. A sample of 54 patients per group was required, and to allow for estimated attrition of 10% we aimed for over-recruitment to 60 patients at each site.

Data management and analysis
All data were double entered into EpiData, cleaned, checked and any discrepancies resolved by reference to the original data collection form. Data were subsequently transferred into Stata v10.0 for analysis.

The study has been analysed and reported using the STROBE guidelines (developed for observational studies from the original RCT CONSORT guidance) (von Elm et al., 2007) as good practice to promote transparency when reporting a non-randomised study.

The primary outcome was pain score, on which the sample size was calculated. Secondary outcomes were total APCA African POS score, and MOS-HIV physical and mental health subscales.

A flow chart was produced to report the numbers of patients screened and recruited. The non-palliative care site is designated “Site 1 (Control)” and the palliative care site “Site 2 (Intervention)”. Sample characteristics were described for each site, and mean APCA African POS and MOS-HIV change scores over time were plotted, and compared between the two groups. The number of deaths at each site was also recorded.

POS item scores were reversed where necessary, so that for all items 0 = no problem in all cases and 5 = worst problem. The seven patient-completed items were summed into a total POS score (possible range 0–35). The two MOS-HIV subscales of mental health and physical health were derived from the MOS-HIV (Revicki et al., 1998).

Change of pain score over time was modelled using multi-level population-averaged logistic regression, adjusting for time and site with an interaction term for random intercept.

Mean scores between week 0 and week 10 were compared using paired t-tests.

Individual-level linear regression models were fitted to find the mean and standard deviation of intercepts by site. The mean slopes were compared between sites using a t-test to observe a difference in change over time. Multi-level linear regression models were fitted both with and without a random intercept, using log likelihood to identify whether the interaction term was a significant improvement.

In order to determine whether CD4 count or ART use was independently affecting outcome change, random-effects maximum likelihood time-series regression models were fitted using site, time, an interaction term, ART use and CD4 count.

Results
Sample characteristics
A total of 60 patients were recruited at Site 1 (Control) and 68 at Site 2 (Intervention) (see Table 1). Of eligible patients, 83.3% and 98.6%, respectively, consented to enter the study. The sample characteristics and completeness of data collection are reported in Table 1. Mean CD4 count was higher at Site 2 (Intervention), with borderline statistical significance
(difference in means = 86, $t = 1.94$, $p = 0.055$). Reporting severe pain and symptoms (rather than one or the other) was more common at Site 1 (Control) (78%) than Site 2 (Intervention) (40%). At Site 1 (Control) no deaths were reported among participants, and at Site 2 (Intervention) 10 deaths were reported.

**Primary outcome**

In population-averaged logistic regression using pain as the outcome (on the possible score range of 0–5, a score of 3, 4 or 5 was coded as significant pain), the odds of significant pain at the two sites were not significantly different at baseline (OR = 0.77, $p = 0.392$). The odds of significant pain reduced by an OR of 0.85 per week (95% CI 0.80–0.90) at Site 1 (Control) and an OR of 0.60 (95% CI 0.50–0.72) at Site 2 (Intervention), which is statistically significantly greater ($p < 0.001$). The outcome improved at both sites, but the improvement was more at Site 2.

**Secondary outcomes**

At baseline, Site 2 (Intervention) had better total POS score ($t = 5.78$), physical health score ($t = -4.95$) and mental health score ($t = -6.82$), which are all significant ($p < 0.001$). These differences reflect the study

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**Table 1. Sample characteristics, baseline scores and data flow.**

<table>
<thead>
<tr>
<th>Site 1 (Control)</th>
<th>Site 2 (Intervention)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n = 60$</td>
<td>$n = 68$</td>
</tr>
</tbody>
</table>

- **Mean age (SD, range)**
  - Site 1: 38.8 years (10.5, 21–76)
  - Site 2: 43.7 years (11.9, 19–76)

- **Gender**
  - Site 1: 82% female
  - Site 2: 66% female

- **Has partner**
  - Site 1: Yes 25%
  - Site 2: Yes 37%

- **No. of children responsible for**
  - Site 1: Median 2.5, range 0–8
  - Site 2: Median 3, range 0–9

- **Mean time since HIV diagnosis (SD, range)**
  - Site 1: 607 days (550, 9–2177)
  - Site 2: 652 days (622, 0–2047)

- **Currently on ART**
  - Site 1: Yes 72%
  - Site 2: Yes 60%

- **Mean CD4 count within last 6 months (SD, range)**
  - Site 1: 255 (180, 1–625)
  - Site 2: 341 (243, 6–946)

- **WHO staging**
  - Site 1: 2% Stage 1
  - Site 2: 9% Stage 1
  - Site 1: 25% Stage 2
  - Site 2: 15% Stage 2
  - Site 1: 62% Stage 3
  - Site 2: 68% Stage 3
  - Site 1: 12% Stage 4
  - Site 2: 9% Stage 4

- **Cancer diagnosis**
  - Site 1: Yes 0%
  - Site 2: Yes 6%

- **Baseline POS pain score (%)**
  - Site 1:
    - No pain = 0: 3.3%
    - 1: 0%
    - 2: 10.0%
    - 3: 15.0%
    - 4: 48.3%
    - Overwhelming = 5: 23.3%
  - Site 2:
    - No pain = 0: 5.9%
    - 1: 1.5%
    - 2: 10.3%
    - 3: 47.1%
    - 4: 29.4%
    - Overwhelming = 5: 5.9%

- **Baseline scores (mean)**
  - POS total score: Site 1 18.95, Site 2 13.43
  - MOS-HIV physical health: Site 1 27.71, Site 2 37.61
  - MOS-HIV mental health: Site 1 33.36, Site 2 46.03

- **Data flow: recruitment**
  - Patients screened at triage: $n = 1365$
  - Reported pain/symptoms at triage: $n = 372$
  - Seen by research nurse and POS scored: $n = 371$
  - Met inclusion criteria: $n = 72$
  - Entered study: $n = 60$

- **Data flow: completion**
  - Week 0: 60
  - Week 2: 59
  - Week 4: 59
  - Week 6: 59
  - Week 8: 60
  - Week 10: 59

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design, i.e., the clinical attention to multidimensional problems using palliative care clinical skills had been introduced to Site 2 (Intervention) prior to recruitment into the study. However, as shown in Table 2, while a statistically significant change (improvement) was found in both sites for POS score and MOS-HIV physical health, this was far greater at Site 2 (Intervention), and while a statistically significant difference (improvement) was found for MOS-HIV mental health at Site 2 (Intervention), none was found at Site 1 (Control). The mean scores in Tables 1 and 2 are slightly different because Table 1 uses all baseline data \((n/C30/128)\) while Table 2 uses only data which can be paired with a week 10 observation \((n/C30/112)\).

Figures 1–3 show the mean total POS score and MOS-HIV subscores over time, with 95% confidence intervals, by site. Plotting the data for all Site 2 (Intervention) patients together and separating out the patients who died at Site 2 (Intervention) (see Figures 1–3) demonstrates that the deaths do not account for the improvements demonstrated (i.e., it was not found that attrition of those with worse health status significantly altered the group mean at the intervention site where 10 deaths occurred). Further, the longitudinal analysis demonstrates that for MOS-HIV physical health, Site 2 (Intervention) participants had better MOS-HIV physical health at baseline and improved more over time. They reported 9.6 points higher (better) physical health at recruitment, and they also gained more per week, slope of 1.46 for Site 2 (Intervention) compared to 0.54 for Site 1 (Control) \((t/C30/C28/C3.15, p/C30/C0.002)\). For MOS-HIV mental health, Site 2 (Intervention) also had better mental health at baseline and improved more over time. They had 12.6 points higher (better) mental health at recruitment, and they also gained more per week, slope of 1.13 for Site 2 (Intervention) compared to 0.26 for Site 1 (Control) \((t/C30/C2.79, p/C30/C0.006)\).

Longitudinal analysis showed that reported total POS score at Site 2 (Intervention) was 5.4 lower (better) at baseline \((p/C30/0.001)\), and that scores improved at Site 1 (Control) by 0.18 per week \((p/C30/0.003)\) but improved by 0.84 per week at Site 2 (Intervention) \((p/C30/0.001\) for difference in change between sites). CD4 count and ART use were not associated with change over time (Table 3).

Similarly, for both MOS-HIV mental and physical health, the score was better at Site 2 (Intervention) at baseline, improved at both sites but with significantly greater improvement at Site 2, and was not associated with CD4 count or ART.

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### Table 2. Change scores.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Site</th>
<th>N</th>
<th>Week 0 (mean, SD)</th>
<th>Week 10 (mean, SD)</th>
<th>Diff. in means</th>
<th>T</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>POS</td>
<td>1 Control</td>
<td>59</td>
<td>18.86 (5.72)</td>
<td>16.39 (7.75)</td>
<td>2.47</td>
<td>2.60</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>2 Intervention</td>
<td>53</td>
<td>12.96 (5.06)</td>
<td>2.15 (2.92)</td>
<td>10.81</td>
<td>14.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physical health</td>
<td>1 Control</td>
<td>59</td>
<td>27.15 (8.91)</td>
<td>32.62 (11.64)</td>
<td>5.47</td>
<td>-4.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>2 Intervention</td>
<td>53</td>
<td>39.16 (12.58)</td>
<td>53.75 (12.93)</td>
<td>14.59</td>
<td>-8.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mental health</td>
<td>1 Control</td>
<td>59</td>
<td>33.15 (9.46)</td>
<td>35.15 (9.68)</td>
<td>2.00</td>
<td>-1.37</td>
<td>0.176</td>
</tr>
<tr>
<td></td>
<td>2 Intervention</td>
<td>53</td>
<td>47.65 (10.71)</td>
<td>59.98 (5.25)</td>
<td>12.32</td>
<td>-8.13</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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Figure 1. POS total score for both sites including and excluding deaths.

Figure 2. MOS-HIV physical health score for both sites including and excluding deaths.
Discussion

These data are the first to report comparative outcomes evaluating palliative care by the existing outpatient staff for HIV outpatients in the presence of ART. The findings demonstrate a clinically and statistically significantly benefit for HIV outpatient care with integrated palliative care involving clinical training, multiprofessional teamwork and the availability of essential drugs. Evidence of high prevalence of pain, symptom and other problems in HIV populations in high-income settings suggest that this model of care should be introduced in these settings.

Although a significant recent body of evidence has demonstrated the high burden of pain, symptoms and other problems, systematic reviews had revealed a dearth of studies evaluating models of HIV palliative care since the 1996 advent of ART (Harding & Higginson, 2005; Harding et al., 2005). Findings from this study offer a substantive response to underpin WHO and UNAIDS clinical policies and guidance that state an essential role for palliative care from the point of diagnosis and alongside treatment, regardless of prognosis. The clinical message from this study is that highly prevalent but poorly controlled multidimensional problems (including pain, symptoms, psychological and existential distress) can be effectively managed under palliative care, and improvement in quality of life can be achieved.

Health economic data are required to determine the cost effectiveness of this training and care. However, the principle of preventing unnecessary suffering and enhancing quality of life and multidimensional well-being through the simple assessment and management of problems in an existing setting offers great promise for replication. Training and clinical support have now been provided to Site 1 (Control) as a result of these data.

There are a number of potential limitations to our study that merit reflection. First, the non-randomised design means that other contextual confounders may have affected results. External validity of the findings should be determined through further replication studies, which is particularly possible in the African context where arguably palliative care has been more readily incorporated into routine HIV care. Second, natural experiment studies are an efficient means of research prior to the heavy investment required for an RCT design, and we took advantage of this opportunity to collect relevant data. However, this lack of a pure experimental design may overinflated the effect

Figure 3. MOS-HIV mental health score including and excluding deaths.

Table 3. Cross-sectional time-series regression models using MLE to find association of site, ART and CD4 count with POS score, mental and physical health score change over time.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Variable</th>
<th>Coefficient</th>
<th>SE</th>
<th>Z</th>
<th>P</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total POS score</td>
<td>Week (Site 1)</td>
<td>−0.18</td>
<td>0.06</td>
<td>−2.93</td>
<td>0.003</td>
<td>−0.30 to −0.06</td>
</tr>
<tr>
<td></td>
<td>Site 2</td>
<td>−5.39</td>
<td>0.97</td>
<td>−5.54</td>
<td>&lt;0.001</td>
<td>−7.30 to −3.48</td>
</tr>
<tr>
<td></td>
<td>Week × Site 2</td>
<td>−0.84</td>
<td>0.09</td>
<td>−9.48</td>
<td>&lt;0.001</td>
<td>−1.01 to −0.66</td>
</tr>
<tr>
<td></td>
<td>CD4</td>
<td>0.00</td>
<td>0.00</td>
<td>0.31</td>
<td>0.760</td>
<td>−0.00 to 0.00</td>
</tr>
<tr>
<td></td>
<td>ART</td>
<td>−0.29</td>
<td>0.91</td>
<td>−0.31</td>
<td>0.753</td>
<td>−2.07 to 1.50</td>
</tr>
<tr>
<td>Mental health score</td>
<td>Week (Site 1)</td>
<td>0.25</td>
<td>0.09</td>
<td>2.74</td>
<td>0.006</td>
<td>0.07 − 0.43</td>
</tr>
<tr>
<td></td>
<td>Site 2</td>
<td>12.12</td>
<td>1.58</td>
<td>7.67</td>
<td>&lt;0.001</td>
<td>9.03 − 15.22</td>
</tr>
<tr>
<td></td>
<td>Week × Site 2</td>
<td>1.04</td>
<td>0.13</td>
<td>7.94</td>
<td>&lt;0.001</td>
<td>0.78 − 1.29</td>
</tr>
<tr>
<td></td>
<td>CD4</td>
<td>0.00</td>
<td>0.00</td>
<td>1.26</td>
<td>0.207</td>
<td>−0.00 to 0.01</td>
</tr>
<tr>
<td></td>
<td>ART</td>
<td>2.48</td>
<td>1.51</td>
<td>1.65</td>
<td>0.100</td>
<td>−0.47 to 5.43</td>
</tr>
<tr>
<td>Physical health score</td>
<td>Week (Site 1)</td>
<td>0.55</td>
<td>0.10</td>
<td>5.54</td>
<td>&lt;0.001</td>
<td>0.35 − 0.74</td>
</tr>
<tr>
<td></td>
<td>Site 2</td>
<td>9.38</td>
<td>2.05</td>
<td>4.59</td>
<td>&lt;0.001</td>
<td>5.37 − 13.39</td>
</tr>
<tr>
<td></td>
<td>Week × Site 2</td>
<td>1.01</td>
<td>0.14</td>
<td>7.17</td>
<td>&lt;0.001</td>
<td>0.73 − 1.28</td>
</tr>
<tr>
<td></td>
<td>CD4</td>
<td>0.00</td>
<td>0.00</td>
<td>1.18</td>
<td>0.351</td>
<td>0.00 − 0.01</td>
</tr>
<tr>
<td></td>
<td>ART</td>
<td>2.37</td>
<td>2.00</td>
<td>1.18</td>
<td>0.237</td>
<td>−1.56 to 6.29</td>
</tr>
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</table>
found for the intervention. Therefore, we have utilised the STROBE method for reporting observational studies (von Elm, et al., 2007), and agree that RCTs may under certain circumstances lack feasibility and external validity (Rothwell & Bhatia, 2007). The unquestioning endorsement of “pure” experimental methods is challenging for evaluation protocols of complex multiprofessional interventions, where blinding is not feasible and the threat of resentful demoralisation is very real (Behi & Nolan, 1996; Berglund, Bolund, Gustafsson, & Sjoden, 1997). Randomisation of patients in participative intervention trials may be self-defeating where effectiveness depends on participation, which in turn depends on subject’s beliefs and preferences (Black, 1996). A common accusation levelled at observational studies is the overestimation of effects. However, reviews of 19 therapies compared findings of RCT vs. observational studies found only two treatments showed differences according to type of study (Benson & Hartz, 2000; Concato, Shah, & Horwitz, 2000). Further, meta-analyses of adverse effects data derived from RCTs as compared to observational studies found that there is no difference on average in the risk estimate of adverse effects of an intervention derived from meta-analyses of RCTs and meta-analyses of observational studies (Golder, Loke, & Bland, 2011).

We support well-designed protocols that select methods according to criteria of feasibility, acceptability and robustness, which may well lead to an RCT design but may also point to prospective quasi-experimental designs. Our analysis plan has investigated and tested alternative explanations for the effect we found. Further, we note the challenges in evaluating our complex intervention which included a multiprofessional team, training and drug availability. While we cannot determine if there is an active ingredient, prior evidence suggests that a focus solely on drug availability may not necessarily influence practice (Logie & Harding, 2005). Lastly, we note the occurrence of 10 deaths at Site 2 (Intervention) and none at Site 1 (Control). We suggest that this is due to their public reputation for having skills in care of the dying through their palliative care provision. The fact that palliative care was in place prior to the commencement of study recruitment means that the intervention site may have been caring for patients closer to death, but that their palliative care skills meant their problems were better managed. It is important to note that our analyses found that the deaths had no significant effect on the mean scores.

In conclusion, this substantive study demonstrates that the addition of simple palliative care training, support and drug availability to standard HIV care and treatment can bring significant improvements in outcomes, for HIV outpatients with ART access.

Acknowledgements

This study was funded by the Diana Princess of Wales Memorial Fund. The study sponsor had no role or involvement in the study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

The authors declare that they have no conflict of interest. We would like to thank the staff and patients of the two participating facilities, the Diana Princess of Wales Memorial Fund for funding this study and Lucy Bradley for manuscript management.

Richard Harding and George Loy conceived the study, Richard Harding, Karilyn Collins, Carla Alexander and George Loy designed the study and Victoria Simms wrote the analysis plan and conducted analysis. Eric Combo and Genevieve Patrick contributed to design and were responsible for recruitment data collection and commented on interpretation. Peter Memiah and Geoffrey Sigalla commented on all stages of design, data collection, analysis and write-up. All authors read and approved the manuscript.

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