Progression of pain in ambulatory HIV-positive South Africans

Noko R Mphahlele (PhD), Peter R Kamerman (PhD), Duncan Mitchell (PhD)

Brain Function Research Group, School of Physiology, Faculty of Health Sciences, University of Witwatersrand, South Africa.

Corresponding author
Peter Kamerman
School of Physiology, Faculty of Health Sciences, University of Witwatersrand, 7 York Road, Parktown, 2193, South Africa, Tel: +27 (0)11 717 2363, Fax: +27 (0)11 643 2765, Email: peter.kamerman@wits.ac.za

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Abstract

Background
Cross-sectional studies report that pain in ambulatory HIV-infected individuals is frequent and often under-managed. Expanding access to HIV treatment in developing countries means that infected individuals are living longer, but there is a dearth of pain-directed studies from developing countries that describe the progression of pain and its treatment over any period of time.

Aim
To characterise the progression of pain and its treatment over a six-month period in ambulatory HIV-positive patients in South Africa.

Methods
We used the Wisconsin Brief Pain Questionnaire to assess changes in pain intensity, pain sites, pain interference and pain treatment over a period of six months in 92 ambulatory HIV-positive patients attending an out-patient clinic in Johannesburg, South Africa.

Results and conclusions
At Visit 1, pain was common (78/92, 85%), and of the patients with pain the majority had moderate or severe pain (67/78, 86%) and pain affected two or more body sites simultaneously (57/78, 73%). After six months, pain prevalence had fallen, but still was high (50/92, 54%), and of those patients with pain at Visit 2, the proportion with moderate or severe pain (41/50, 82%), or two or more pain sites (32/50, 62%) had decreased. Analgesic use was low at both time-points (5% and 25% analgesic use at Visit 1 and 2, respectively). Despite the high pain burden, pain interference in daily activities was very low across the time period assessed. The burden of pain in our cohort of ambulatory HIV-positive patients was high, but there were significant reductions in pain burden over time.

Key words
pain intensity, pain interference, pain management, pain undertreatment
Introduction

Pain associated with HIV infection is common and may arise from the actions of the virus itself, from secondary consequences of immune suppression, as side effects of medication, from depression, or be incidental to the infection (Kamerman & Mitchell, 2011). Multiple, potentially co-existing, causes of acute and chronic pain complicate the identification and management of pain in HIV-infected patients. This situation is exacerbated by the lack of an armamentarium of analgesics with proven efficacy in treating HIV-related pain (Clifford et al., 2012; Kamerman & Mitchell, 2011; Phillips, Cherry, Cox, Marshall, & Rice, 2010). If pharmacological pain management is employed, it frequently is inadequate (Kamerman & Mitchell, 2011; Maree et al., 2010). The lack of proven treatments and the complicated nature of pain in HIV means that it is essential to know how pain progresses in patients with HIV infection, especially now that modern antiretroviral therapy has added decades to the lives of those infected with HIV. Better awareness amongst nursing professionals of HIV-related pain and its progression is especially important in the context of increased task-shifting of HIV diagnosis, treatment and monitoring to nurse-led HIV and primary care clinics, particularly in sub-Saharan Africa (Callaghan, Ford, & Schneider, 2010; Zachariah et al., 2009).

Only a few pain-directed studies of progression of pain in ambulatory HIV-infected individuals have been published, and they typically have reported that pain increased (de Boer, Prins, Sprangers, Smit, & Nieuwkerk, 2011) or was stable (Saunders & Burgoyne, 2002; Tsao, Dobalian, & Stein, 2005) over time. One comprehensive study did reveal pain attenuation over time, but by only one point, on average, on an 11-point scale, and left the patients in moderate pain, on average, after five years (Koeppe, Lyda, Johnson, & Armon, 2012). All these studies were conducted in developed countries, which contribute only a small proportion of the total global HIV burden, and do not reflect the ethnic, sex and socio-economic characteristics of the majority of people infected with the virus (Joint United Nations Programme on HIV/AIDS, 2010). In developing regions, sub-Saharan Africa in particular, HIV-associated pain is just as prevalent and serious in ambulatory patients as it is in developed countries (Mphahlele, Mitchell, & Kamerman, 2012; Namisango et al., 2012; Parker, Stein, & Jelsma, 2014). But we do not know how pain progresses in these patients, in intensity or site of presentation, or whether such patients are offered any form of ongoing pain management. We do have hints though from assessments of pain, as one of many symptoms, in studies of quality of life of patients with chronic HIV infection. In every one of these studies, the prevalence of pain dropped when the sub-Saharan patients entered treatment (Fox et al., 2010; Jelsma, Maclean, Hughes, Tinise, & Darder, 2005; Rosen et al., 2010; Rosen, Ketlhapile, Sanne, & Desilva, 2008; Stangl, Wamai, Mermin, Awor, & Bunnell, 2007). We therefore investigated the change in pain intensity, pain sites, pain interference and pain treatment over a period of six months, in South African ambulatory HIV-positive patients, some of whom were on antiretroviral therapy at entry, some
who began therapy during the six months, and some who never received antiretroviral therapy. The population studied is broadly representative of the clinic population that would be encountered in nurse-led primary care and HIV clinics in sub-Saharan Africa.

Methods
Research questions
Does the prevalence, burden (pain intensity, number of pain sites, pain interference), and treatment of pain change over a six-month period in South African ambulatory HIV-positive patients attending a public-sector out-patient clinic?

Sample
The research was approved by Human Research Ethics Committee (Medical) of the University of the Witwatersrand, South Africa, according to the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. All participants provided written informed consent.

We initially recruited a convenience sample of 92 ambulatory HIV-positive outpatients from the Themba Lethu Clinic, Helen Joseph Hospital, Johannesburg, South Africa, from March 2005 to July 2006. Participants were recruited while they were waiting to see a doctor during their routine clinic visits and without consideration for whether they were, or had been in pain or not. Inclusion criteria were age 18 years or older, a confirmed diagnosis of HIV infection, outpatients, and able to comprehend the interview in English, isiZulu, isiXhosa, Sepedi, Setswana or Xitsonga.

Setting
A detailed description of the Themba Lethu Clinic has been reported by Fox and colleagues (2013). In brief, the clinic is a public sector clinic for HIV-infected individuals at a metropolitan secondary hospital in Johannesburg, South Africa. The clinic is staffed by between six and eight full-time medical doctors, nine nurses, and three pharmacists. The clinic services a total cohort of about 4600 HIV-positive patients not on antiretroviral therapy, and about 12 400 patients receiving antiretroviral therapy. Between 400 and 500 patients attend the clinic per day. Two-thirds of the cohort are female, and over 90% are of African ancestry.

Study Procedure
All patients were interviewed about their pain at the time of recruitment (Visit 1), and requested to return for a similar interview six months later (Visit 2). Basic demographic information (age, sex, ancestry, years of education, employment status) was obtained from all participants. We used the Wisconsin Brief Pain Questionnaire, which we had translated into local languages and validated previously for use in South African HIV-positive patients (Mphahlele, Mitchell, & Kamerman, 2008), to characterise each patient’s pain and the extent to which it interfered with
daily function. Because some of the patients were not sufficiently literate to complete forms themselves, trained interviewers administered the questionnaire to all participants using a standardized interview technique. Patients’ medical histories (CD4 T-cell count and medications) were obtained through personal recall, and these data were confirmed and supplemented from hospital records. The patients used an 11-point scale (0 = ”no pain”, 10 = ”pain as bad as you can imagine”) to rate pain intensity at the time of interview, without us attempting to resolve HIV-related pain from incidental pain. They rated the extent to which current pain interfered with functionality (mood, sleep, enjoyment of life, relations with others, walking ability and normal work) on a five-point scale (0 = “no interference, 4 = ”extreme interference”). They also marked all current pain sites on a cartoon of body outline.

**Data Analysis**
Demographic, HIV disease, and pain characteristics of the cohort at baseline (visit 1) were summarised as mean and 95% confidence interval (age), median and 95% confidence interval (pain intensity), or the percentage of participants with a characteristic (female sex, level of education, no income, receiving antiretroviral therapy, range of CD4-T cell count, had pain, two or more pain sites). Our data presentation and analysis for the progression of pain over the six-month period between the two assessments was based on the 95% confidence interval of medians or proportions of compared groups. If the 95% confidence intervals of the difference did not span zero, the difference was considered statically significant. All analyses were completed using Microsoft Excel 2010, with confidence interval calculations implemented using a confidence interval calculator macro (Herbert, 2013). On the basis of their pain intensity at the time of interview, we considered the patients to have no pain (score = 0), mild pain (score = 1-3), moderate pain (score = 4-7) or severe pain (score = 8-10).

**Results**
**Patient Sampling**
The demographic details of our cohort are summarised in Table 1. The majority of the cohort were female, were on antiretroviral therapy, and had pain.

**Changes in Pain Prevalence and Intensity**
Table 2 summarizes the change in pain intensity over six months for the cohort of 92 patients as a whole, and subdivided according to the intensity of the pain they were experiencing at Visit 1. For the cohort as a whole, pain prevalence fell from 78/92 (85%) patients to 50/92 (54%) between Visit 1 and Visit 2. Three of the fourteen patients (21%) who did not have pain at Visit 1 developed pain by Visit 2, and seven (20%) of patients with moderate pain at Visit 1 had severe pain at Visit 2. By contrast, 31/78 patients (40%) who had pain at Visit 1 no longer had any pain six months later. Pain intensity decreased significantly for those patients with moderate or severe pain at Visit 1, but there was no significant change in intensity for the patients who had no pain or mild pain at Visit 1.
Pain Sites
Table 3 shows the number of patients with zero, one, or two and more pain sites at Visit 1 and six months later, grouped according to their pain intensity (mild, moderate or severe) at Visit 1. Pain affected two or more body sites simultaneously in 73% (57/78) of patients with pain at Visit 1, decreasing to 62% of patients with pain at Visit 2 (32/50). For no category of initial pain did the number of sites increase significantly over the six months. For patients who started with moderate or severe pain the number with pain at two or more sites decreased significantly. Of the three patients without pain at Visit 1, but who developed pain by Visit 2, two developed pain at two or more sites. The three most common pain sites at Visit 1 and Visit 2 were the head, chest and feet.

Pain Interference
Patients reported low interference (median = 1, interquartile range 0-2, on a scale of 0 to 4) at the first visit, even though a third were in severe pain then. At their second visit after six months, and irrespective of their pain intensity then, more than half the patients reported that their residual pain imposed no interference at all with their functionality.

Pain Management
Figure 1 shows the types of analgesic therapy prescribed to patients who reported pain at Visit 1, and to the same patients six months later. At Visit 1, only 4 patients (5%) of the 78 patients in pain received any analgesic treatment, in all cases non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol. Of the 48 patients still in pain at Visit 2, 36 (75%) were not being prescribed any form of analgesic, with the remainder being prescribed an NSAID, a tricyclic antidepressant (amitriptyline), or a combination of an NSAID and a tricyclic antidepressant. Of the 30 patients who no longer were in pain after six months, only one was receiving an analgesic, amitriptyline.

Pain Progression and Antiretroviral Therapy
There was no significant difference in median pain intensity between the 60 patients on antiretroviral therapy and the 32 not on antiretroviral therapy at Visit 1. Six months later, the median pain intensity of the 80 patients then on antiretroviral therapy was four points lower than that of the 12 patients not on antiretroviral therapy. Being on antiretroviral therapy at both visits (n = 55) was associated with a significant reduction in number of patients in pain, and in patients with pain at more than one site, in median pain intensity, and in number of patients with chest pain, between visits (Table 4). Only seven patients were not on antiretroviral therapy at either visit, and none of their pain characteristics changed significantly between visits.

Discussion
We investigated changes in pain intensity, prevalent pain sites, number of pain sites, pain interference and analgesic usage over a six-month period in 92 HIV-positive South Africans.
attending a public sector HIV clinic. To our knowledge, ours is the first longitudinal study in Africa that has examined changes in pain intensity, pain sites and analgesic use in HIV-positive patients. All of our patients had access to antiretroviral therapy and about two-thirds were on antiretroviral therapy at the first interview. Only 5% of the patients reporting pain were on any analgesic therapy at the beginning of our study. After six months, proportionally more patients were receiving analgesics, but three-quarters of those then reporting pain were still receiving no opioids. Though some patients were in severe pain throughout the six months, none received opioids. So it is very unlikely that any changes in pain characteristics, at least for those in moderate or severe pain, could be attributed to appropriate analgesic therapy. Only one of the patients who were not in any pain after six months was receiving any analgesic, so their absence of pain likely had little to do with successful ongoing analgesic therapy.

Most of our patients were in pain at the beginning of our study, and of those, most were in moderate to severe pain at multiple pain sites simultaneously. However, what we saw in our cohort was a massive reduction in the burden of pain over the six months, with a third of patients being pain free after six months. Thus, not only was the reduction in the burden of pain in our patients very substantial, but it was quick. The patients that improved most were those who started with moderate to severe pain, and who had pain at more than one body site. In spite of those patients on antiretroviral therapy receiving stavudine, which is associated with the development of peripheral neuropathy (Kamerman, Wadley, & Cherry, 2012), the proportion of patients with foot pain dropped over the six months.

Pain in HIV-infected individuals has been reported to be unrelated to whether they were on antiretroviral therapy or not (Mphahlele et al., 2012), such that therapeutic increases in CD4 T-cell count provide no guarantee that HIV-related pain will be relieved (Kamerman & Mitchell, 2011). The question arises therefore as to whether the decrease in the pain burden was associated with ongoing antiretroviral therapy over the six months. Being an antiviral therapy was associated with improvement in many pain parameters (Table 4), none of which changed in patients never on antiviral therapy, although our sample of patients never on antiviral therapy in the six months was small.

Though for most patients in our cohort the burden of pain was reduced over the six months, some remained in pain, and even in severe pain. Even though pain may not have resolved for everyone, suffering appears to have resolved for most. More than half the patients, including some still experiencing moderate-to-severe pain, reported no interference at all with functionality after six months. We have remarked previously how stoical our patient population is (Mphahlele et al., 2012), a sentiment we endorse now. However, patient stoicism is not a justification for poor pain management.
As is typical for cohorts of HIV-positive patients in sub-Saharan Africa, our cohort consisted predominantly of women (82%) with no education past secondary school, and with half the cohort having no income. There have been estimates of how pain prevalence progresses in such patients, based on questionnaire items in more-general assessments of quality of life. Some of these assessments have been based on validated instruments such as the EQ-5D (Jelsma et al., 2005) and MOS-HIV (Stangl et al., 2007), but others on custom-made (and apparently unvalidated) instruments (Fox et al., 2010; Rosen et al., 2010, 2008). All these studies, like ours, report that the prevalence of pain dropped over time. Unlike ours, none of the studies explored intensity or sites of pain, or potential benefits of analgesia. Like ours, all the studies have drawn attention to the distressingly high number of HIV-positive patients who remain in pain even after years of antiretroviral therapy, with many re-entering employment while still in pain (Rosen et al., 2010).

There have been pain-directed longitudinal studies in ambulatory HIV-positive patients in developed countries (de Boer et al., 2011; Koepppe et al., 2012; Saunders & Burgoyne, 2002; Singer et al., 1993; Tsao et al., 2005), and in these studies the burden of pain did not necessarily diminish over time. In a cohort of Dutch patients followed up for five years, all painful symptoms increased over time (de Boer et al., 2011). In two cohorts of US patients, existing pain was stable for up to two years (Saunders & Burgoyne, 2002; Tsao et al., 2005), and, in one of those cohorts, nearly half the patients asymptomatic at entry developed pain within two years (Saunders & Burgoyne, 2002). There is one comprehensive five-year study of 127 ambulatory US HIV-positive patients that, like our study, does address pain intensity, pain sites and analgesia (Koepppe et al., 2012). Those patients did exhibit reduced pain intensity, but it was marginal, from an average of 5/10 initially to 4/10 after five years. This study, however, did involve patients identified as having chronic pain. No consistent and readily identifiable reasons that explain the discrepancies between studies have been identified.

**Limitations**

It was a potential limitation of our study that we followed the patients up only at six months. Pain progression in ambulatory HIV-positive patients has been followed for as long as five years in the USA (Koepppe et al., 2012), and quality of life, including some assessment of the impact of pain, for three years in the community from which our patient population came (Rosen et al., 2010). It is a feature of all the studies of quality of life in HIV-positive patients in sub-Saharan African countries that the major improvement in pain prevalence occurs within the first three months of initiation of management (Beard, Feeley, & Rosen, 2009; Rosen et al., 2008; Stangl et al., 2007), with pain creeping back, from its attenuated level, in some patients after two years (Fox et al., 2010). So even though we studied pain progression over six months only, we believe that we had seen the bulk of the changes likely to occur. A second potential limitation is that by soliciting information on their pain we may have inadvertently contributed to the reduction in the patients’ pain through a “care effect”. A non-specific “care effect” resulting from positive
interaction between medical practitioner and patient has been reported in a variety of settings, including pain management (Hojat et al., 2011; Kaptchuk et al., 2008; Rakel et al., 2009), and this benefit also may have accrued to patients in our cohort. Finally, a limitation that applies to the field in general, is that in the absence of reliable information about the prevalence of pain in HIV-negative members of the same resource-poor communities, it is not possible to decide whether the residual prevalence of pain in treated HIV-positive patients still exceeds the background prevalence for their communities. In our study, and those of others (Fox et al., 2010; Rosen et al., 2010, 2008; Stangl et al., 2007), prevalence appears to remain higher than background, but prevalence may have attained background prevalence (around 33%) in the community studied by Jelsma and colleagues (Jelsma et al., 2005).

**Implications for Nursing**

We believe that our findings have implications for nursing pain management training and practice in the busy HIV clinics of sub-Saharan Africa. Firstly, our finding that minimal analgesic medication was offered to patients in pain indicates that very little attention was being paid to pain management in the clinic. Successful pain management, especially in nurse-led primary care environments, requires that nurses are aware of the need for routine and repeated pain assessment in HIV-positive patients, even in those patients who are ambulatory and on stable antiretroviral therapy. This need for routine pain assessment has to be coupled with nurses being trained in the basic skills of assessing pain and deciding on appropriate management (e.g., prescribing pain medications as allowed, or referring cases if more highly controlled medications are required or it is a complicated case) (Ekim & Ocakci, 2013; McCaffery & Ferrell, 1997; Voshall, Dunn, & Shelestak, 2013). Importantly, where nurses are allowed to prescribe basic pain medications (e.g., acetaminophen and non-steroidal anti-inflammatory drugs), they need to be educated on the need for sufficient medication to be prescribed and dispensed to patients until their next clinic appointment (Maree et al., 2010). Pain management education for nurses can make a difference in the pain experienced by the patients (Long, 2013).

Furthermore, the significant reduction in pain and suffering experienced by our patient group, despite inadequate pharmacotherapy, may be indicative of a “care-effect”, which has been described by in a variety of different clinical settings (Hojat et al., 2011; Kaptchuk et al., 2008; Rakel et al., 2009). Indeed, the psychosocial drivers of pain in HIV-positive individuals are likely to be complex, but awareness should be raised amongst nurses that merely enquiring empathetically after a patient’s pain may have significant therapeutic benefit. Although we did not assess feelings, thoughts and belief about pain, exploring and discussing the experience of pain and the associated losses in our stoical patient group may have allowed the patients to move towards acceptance of their life situation (Haraldseid, Dysvik, & Furnes, 2014). Patient stoicism and the “care effect” are active areas of research in our laboratory.
Conclusion
In summary, in the first pain-directed study of pain progression in HIV-positive patients in a resource-poor community we have shown that the burden of pain in HIV-positive out-patients is not static. In our study pain was significantly reduced over a six-month follow-up period despite inadequate pharmacological treatment of the pain. Indeed, the reasons for the reduction in pain are far from certain, and the matter requires further investigation.

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Figure Legend

Figure 1: Types of analgesic therapy prescribed to patients in pain at visit 1 (n = 78; A), to patients who were still in pain six months later (n = 48; B), and those patients who no longer were in pain six months later (n = 30; C). TCA: tricyclic antidepressant.
A

No analgesics: 95%

B

No analgesics: 75%

C

No analgesics: 97%
Table 1: Characteristics of 92 ambulatory HIV-positive individuals

| Description                                      | Visit 1 |
|--------------------------------------------------|---------|
| Age (mean, 95% CI)                               | 35 (21 to 65) |
| Female (%)                                       | 82      |
| Education (%)                                    |         |
| No education                                     | 3       |
| Primary*                                         | 10      |
| Secondary†                                       | 84      |
| Tertiary                                         | 3       |
| Patients with no income (%)                      | 50      |
| Patients initially on antiretroviral therapy (%) | 65      |
| Patients with pain (%)                           | 85      |
| Pain intensity (median, 95% CI)                  | 6 (0 to 10) |
| Patients with pain at more than one site (%)     | 63      |
| Patients CD4 T-cell ranges (%)‡                  |         |
| < 200 cells/mm³                                   | 53      |
| 200 – 499 cells/mm³                              | 45      |
| ≥ 500 cells/mm³                                  | 2       |

*: Estimated age: 6-13 years,
†: Completed secondary school,
‡: CD4 T-cell count measured at the time of the interview (n = 51)
| Pain intensity at Visit 1 | n   | Median pain intensity (interquartile range) | 95% CI of the difference in the median between Visit 1 and Visit 2 | Direction of change |
|--------------------------|-----|---------------------------------------------|-----------------------------------------------------------------|--------------------|
| All                      | 92  | 6 (3 to 9)                                  | 2 to 8                                                          | NS                 |
| Severe to moderate       | 4   | 0 to 10                                     | 5 (0 to 10)                                                     |                   |
| Moderate to mild         | 2   | 1 to 0                                      | 0 (0 to 0)                                                      |                   |
| NS                       | 2   | 0 (0 to 0)                                  | 0 (0 to 0)                                                      |                   |
| Moderate pain            | 35  | 6 (4.5 to 6.5)                              | 2 to 6                                                          |                   |
| NS                       | 3   | 2 (0 to 5)                                  | 0 (0 to 0)                                                      |                   |
| Mild pain                | 14  | 1 (4)                                       |                                                                  |                   |
| Severe to moderate       | 32  | 10 (9 to 10)                                | 4 to 10                                                         |                   |
| NS                       | 11  | 2 (0 to 5)                                  |                                                                  |                   |

Table 2: Change in pain intensity over six months for all patients, and subdivided according to pain intensity at Visit 1. Bolded values: number of patients that were in the same category at Visit 1 and Visit 2. NS: No significant change.
Table 3: Number of pain sites at Visit 1 and Visit 2, subdivided according to pain intensity at Visit 1

| Pain intensity | Number of pain sites | Number of patients (%) | 95% CI of the difference in the percentage between Visit 1 and Visit 2 | Direction |
|----------------|----------------------|------------------------|---------------------------------------------------------------------|------------|
| No pain        | 0                    | 14 (100)               | 11 (47) 0 0 0                                                    | NS         |
| SN             | 0                    | 0 (0)                  | 2 (3) 1 0 0                                                    | NS         |
| Increase       | 3                    | 2 (14)                 | 1 (7) 0 0                                                     | NS         |
| Decrease       | 1                    | 0 (0)                  | 1 (7) 0 0                                                     | NS         |
| Mild pain      | 0                    | 0 (0)                  | 15 (41) -23                                                    | Increase   |
| SN             | 4                    | 4 (36)                 | 3 (27) 0 0                                                   | NS         |
| Increase       | 9                    | 9 (24)                 | 8 (24) 0 0                                                   | NS         |
| Decrease       | 7                    | 7 (93)                 | 12 (16) 0 0                                                   | NS         |
| Moderate pain  | 0                    | 0 (0)                  | 15 (41) -23                                                  | Increase   |
| SN             | 5                    | 5 (43)                 | 3 (27) 0 0                                                   | NS         |
| Increase       | 26                   | 26 (76)                | 12 (32) 0 0                                                  | NS         |
| Decrease       | 12                   | 12 (32)                | 15 (41) -23                                                 | NS         |
| Severe pain    | 0                    | 0 (0)                  | 11 (34) -17                                                  | Increase   |
| SN             | 2                    | 2 (17)                 | 1 (7) 0 0                                                   | NS         |
| Increase       | 11                   | 11 (86)                | 9 (24) 0 0                                                   | NS         |
| Decrease       | 4                    | 4 (36)                 | 7 (54) 0 0                                                   | NS         |

Table 3: Number of pain sites at Visit 1 and Visit 2, subdivided according to pain intensity at Visit 1.
| Decrease | 1 to 45 | 16 (50) | 24 (75) | ≥ 2 |
|----------|---------|---------|---------|-----|
| NS       | 11 to 29 | 5 (16)  | 8 (25)  | 1   |

NS: No significant change
### Table 4: Pain characteristics for patients who were on antiretroviral therapy at Visit 1 and at Visit 2, six months later (n = 55)

| Description                                      | Visit 1 | Visit 2 | 95\% CI of the difference | Direction of change |
|--------------------------------------------------|---------|---------|----------------------------|---------------------|
| Patients with pain (%)                           | 85      | 51      | 17 to 49 %                 | Decrease            |
| Pain intensity (median)                           | 6 (0 to 10) | 2 (0 to 10) | 2 to 6 | Decrease |
| Patients with pain in more than one site (%)     | 56      | 35      | 32 to 38 %                 | Decrease            |
| Pain interference (median)                        | 1       | 1       | NS                         | NS: No significant change |
| Patients not on analgesics (%)                    | 95      | 96      | NS                         | Decrease            |