Pain in people living with HIV and its association with healthcare resource use, well-being and functional status

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Pain in people living with HIV and its association with healthcare resource use, well-being and functional status

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Abstract

Objective: We describe the prevalence of pain and its associations with healthcare resource utilisation and quality-of-life.

Design: The POPPY Study recruited three cohorts: older PLWH (≥50 years, n=699), younger demographically/lifestyle similar PLWH (<50 years, n=374) and older demographically/lifestyle similar HIV-negative (≥50 years, n=304) people from April 2013-February 2016.

Methods: Current pain and pain-related healthcare use was collected via a self-reported questionnaire. Logistic regression assessed between-group differences in the prevalence of pain in the past month and current pain after controlling for potential confounders. Associations between current pain and healthcare resource use, reported joint problems, depressive symptoms, quality-of-life and functional status were assessed in PLWH using Mann-Whitney U and Chi-squared tests.

Results: Pain in the past month was reported by 473/676 (70.0%) older PLWH, 224/357 (62.7%) younger PLWH and 188/295 (63.7%) older HIV-negative controls (p=0.03), with current pain reported in 330 (48.8%), 134 (37.5%) and 116 (39.3%), respectively (p=0.0007). Older PLWH were more likely to experience current pain, even after adjustment for confounders. Of those with pain in the past month, 56/412 (13.6%) had missed days of work or study due to pain, and 520 (59%) had seen a doctor about their pain. PLWH experiencing current pain had more depressive symptoms, poorer quality-of-life on all domains, and greater functional impairment, regardless of age group.

Conclusions: Even in the effective ART era, pain remains common in PLWH and has a major impact on quality-of-life and associated healthcare and societal costs. Interventions are required to assist clinicians and PLWH to proactively manage pain.

Key words: HIV; pain; quality of life; depressive symptoms

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Conflict of interest

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Introduction

The widespread use of antiretroviral treatment (ART), and an increased focus on engagement and retention in care, has meant that people living with HIV (PLWH) in many parts of the world now have a near-normal life expectancy, particularly if a good CD4 cell count response and undetectable viral load are achieved on ART [1,2]. However, the cohort of PLWH is ageing: for example, recent data from the Netherlands suggest that by 2030, almost three-quarters of PLWH will be aged 50 years or older, with the prevalence of age-associated co-morbidities (such as cardiovascular disease, diabetes, chronic kidney disease, osteoporosis and non-AIDS malignancies) and use of concomitant medications also expected to increase [3].

Moderate or severe pain has, in some studies, been reported to be one of the most common physical symptoms among PLWH, with reported prevalence ranging from 30% to 83% [4-8], and reports of high rates of several pain-related conditions among PLWH in Western countries [9-12]. Pain among PLWH has both clinical and public health importance. Not only is pain associated with psychological distress, emotional problems, poor quality-of-life and suicidal ideation [13-17], but it is also known to impact on activities of daily living [18] and is associated with higher rates of sick leave, job loss and lower satisfaction with health care [19]. Among PLWH, pain is associated with poorer adherence to ART [20, 21], higher rates of viral load rebound [22], treatment switching [23, 24] and, in some subgroups, missed clinic visits [25]. Furthermore, PLWH in pain are more likely to experience lack of social support [26] and to be involved in risky behaviours such as alcohol use, intravenous drug use and sexual risk taking [6, 27-30]. Thus, in addition to the burdens placed on both the individual and the healthcare/social system, pain in PLWH has the potential to seriously curtail attempts to eliminate new HIV infections.

Despite this, chronic pain is, however, mostly neglected in clinical practice and little research has been conducted on the topic in the modern ART era among individuals in whom HIV infection is largely controlled. Yet, effective interventions for pain are available which could lead to substantial benefits if used appropriately. We describe the prevalence of pain, associated factors and association with healthcare resource utilisation and quality-of-life among PLWH and demographically and behaviourally similar HIV-negative controls.

Methods

POPPY is a prospective cohort study at seven clinical sites in the UK and Ireland that aims to investigate the impact of HIV on the development and outcomes of comorbidities and pharmacotherapy among older PLWH [31]. Three sub-groups are studied within POPPY: older HIV-positive (≥50 years old, n=699), younger HIV-positive (<50 years, n=374) and older HIV-negative (≥50 years old, n=304) people. Eligible HIV-positive participants acquired HIV through sexual transmission (either sex between men or sex between men and women – those acquiring HIV through other routes, including injection drug use, were excluded), were cisgender, and were either of white or black African ethnicity. Those recruited to the younger group of PLWH were frequency-matched to the group of older PLWH on gender, ethnicity, sexual orientation and participating clinic. HIV-negative participants were required to have a documented negative HIV testing; this group was frequency-matched to the older PLWH group on age, gender, ethnicity, sexual orientation and geographical location (in or out of London). The study was approved by the UK National Research Ethics Service (NRES; Fulham, London, UK; reference number 12/LO/1409) and written informed consent was obtained from all participants.

The POPPY dataset includes information on socio-demographics, pharmacotherapy, family history, medical history, healthcare utilisation and quality-of-life. The POPPY dataset is linked to the UK Collaborative HIV Cohort (UK sites [32]) and to the UCD ID Cohort (Dublin [33]) for historic data on ART and longitudinal data on CD4 counts and HIV RNA. A self-completed questionnaire [5] asks about experience of aches or pains that have lasted one day or longer in the past month, whether the pain is current, the bodily site of any pain, whether it has resulted in any missed days from work, or whether it has resulted in the participant consulting their family doctor; responses to each of these questions are either 'yes' or 'no'. Information on pain and related resource-use is also available through the data captured on concomitant medication use (including specific use of a range of analgesics, reported as free-text), self-reported medical conditions (including a history of joint problems, joint inflammation, rheumatoid/osteo-arthritis, joint replacement, aches/pains and back pain), and reported visits to the GP, pain clinics or other specialist services for reasons relating to pain over the past year. Information on quality-of-life is collected via the SF-36 questionnaire [34], with depressive symptoms assessed through use of the Center for Epidemiologic Studies Depression (CES-D) questionnaire [35] (score ≥16 indicative of significant depression), and Patient Health Questionnaire-9 (PHQ-9) questionnaire [36]

(score ≥5 indicative of current depression). The Lawton Instrumental Activities of Daily Living (IADL) questionnaire [37] is used to assess functional status; participants are considered as fully functional if they have a score of ≥8 on this scale. The present analyses used cross sectional data from the baseline POPPY visit only, conducted between April 2013 and February 2016.

Statistical analysis

The proportions of participants in the three POPPY study groups reporting any aches and pains in the past month, and reporting current pain, were compared using Chi-squared tests and logistic regression, with and without adjustment for gender, sexuality, race, educational level and body mass index (BMI, calculated as weight/height^2) all assessed at the baseline visit. Although we also describe associations with working status, this was not incorporated into multivariable regression analyses due to the difficulties in assessing the direction of any association. Associations of current pain with quality-of-life, depressive symptoms and IADL in the subgroup of PLWH were assessed using Mann Whitney U tests and Chi-squared tests, after stratification by age group (these analyses did not include the group of HIV-negative controls given the strong impact of HIV infection on these outcomes). All analyses were performed using SAS v9.3 (SAS Institute Inc., Cary, NC).

Results

Prevalence of pain

Information on pain was available for 1325 of the 1377 (96.2%) POPPY participants (Table 1), 676 of older PLWH, 357 younger PLWH and 292 HIV-negative controls. Those for whom information on pain was available were more likely to be male (81.1% vs. 65.4%, p=0.008), men who have sex with men (MSM, 70.6% vs. 53.9%, p=0.02), of white ethnicity (86.1% vs. 65.4%, p=0.0001), and had been recruited in the earlier years of the study (58.4% recruited in 2013/2014 vs. 44.2%, p=0.04). Furthermore, the median age of those with information on pain was slightly lower at 54 years vs. 51 years in those without information on pain (p=0.05). Among PLWH, 1011 (97.9%) of those with pain information available were on ART, 925 (90.0%) had a viral load $\leq$50 copies/ml, and median latest and nadir CD4 counts were 626 and 203 cells/mm^3, respectively, with no significant differences from those without information available.

The prevalence of reported aches and pains in the last month was 66.6% (882/1325) and was significantly higher in older PLWH (473/676, 70.0%) than in either younger PLWH (224/357, 62.7%) or older HIV-negative controls (188/295, 63.7%, p=0.03). Those who reported pain in the past month were more likely to be female (p=0.01), heterosexual (p=0.02), of black African ethnicity (p=0.01) and were slightly older (p=0.01) than those not reporting pain (Table 1). Those reporting pain in the past month also had lower educational attainment (p=0.002) than those not reporting pain in the past month. In unadjusted analyses, and compared to older PLWH, the odds of reporting aches or pains in the last month was 28% lower in younger PLWH, and 26% lower in HIV-negative controls (Figure 1a); after adjustment for potential confounding factors, associations between the three groups remained significant (Figure 1a).

Of those reporting pain in the past month, pain was reported to be current in 580 (43.8% of those with information on pain, Table 1). Current pain was again more common in the older PLWH (330/676, 48.8%) than in younger PLWH (134/357, 37.5%), or older HIV-negative controls (116/292, 39.7%). Associations with demographic factors, work and educational status were broadly similar to those seen for any pain in the past month. In unadjusted analyses, and compared to older PLWH, the odds of reporting current pain was 37% lower in

younger PLWH and 31% lower in HIV-negative controls (Figure 1b) with associations again remaining significant after adjustment for potential confounders (Figure 1b).

In the two groups of PLWH, of the HIV factors, only a lower nadir CD4 count was associated with an increased risk of either pain in the past month or current pain in the two groups of PLWH, with no associations being seen with either ART exposure or current CD4 count (Table 1). Adjustment for nadir CD4 count did not modify the association between age group and either any pain in the past month or current pain in PLWH (Figures 1a/b).

Impact of pain on daily activities and resource use

Of those reporting pain who provided a response, 13.6% (56/412) reported having missed days of work or study due to the pain; 18.9% (30/159) in older PLWH, 12.2% (17/139) in younger PLWH and 7.9% (9/114) in HIV-negative controls (p=0.03). When we compared current work status, only 41.7% of those reporting current pain were working full-time, compared to 62.7% of those not reporting current pain. Whilst similar (small) proportions in the two groups were students (1.4% vs. 1.1%, respectively), 30% of those reporting current pain were unemployed or on sick leave (vs. 14.8% in those not reporting current pain) and 26.9% were classified as having other or unknown work status (vs. 21.5% of those not reporting current pain, global p=0.0001). Fifty-nine percent of participants had seen a doctor about their pain (295 (62.4%), 110 (49.1%) and 115 (62.2%) in the three groups respectively, p=0.002). Pain-related resource use is shown in Table 2. Reported analgesic use was more common in older PLWH than in the other two groups. Although there were significant between-group differences in reported joint problems, GP visits and any pain-related resource use, these differences appeared to be driven more by older age than by HIV status. GP visits for pain were lower in the two groups of PLWH than in HIV-negative controls.

PLWH experiencing current pain had significantly higher scores on both CES-D and PHQ-9, regardless of age group, reflecting greater levels of depressive symptoms (Table 3). Almost all domains of quality-of-life were poorer in those experiencing current pain than in those without current pain. Individuals in both age groups experiencing current pain were also less likely to be classified as fully functional on the Lawton IADL score.

Discussion

Despite the use of more modern ART regimens, older PLWH continue to experience higher rates of pain than similarly-aged HIV-negative participants. Interestingly, whilst younger PLWH also reported a high rate of pain, this was at a similar level to that seen among the older HIV-negative participants. In all three groups, pain was associated with lower employment rates and with high levels of healthcare resource use. Among the two groups of PLWH, current pain was associated with higher depressive symptoms, poorer quality-of-life and poorer functional status, regardless of age.

Pain has frequently been reported to be one of the most common symptoms among PLWH, particularly in the pre- and early-combination ART eras. In a review article of 28 studies published from 1993-2011, Parker [6] reported a weighted point prevalence of pain of 54% and a three-month pain prevalence rate of 83%. Whilst more recent years have seen improvements in both the efficacy of ART, and the range of ART drugs that are available for use, pain continues to be frequently reported [4, 5, 8]. Among participants in the Women's Interagency HIV Study (WIHS), 56.1% indicated experiencing pain for at least 6 days over the past 6 months, with one in ten participants reporting experiencing pain for >120 days and over a third reporting experiencing extreme pain at least once over the period [38]. Pain in PLWH is also complex; in one study of attendees at a primary care clinic in New York City [39], the most common pain disorders reported were musculoskeletal pain, followed by neuropathic pain, headaches (including migraine), other poorly defined pain syndromes and chronic pelvic pain; multiple chronic pain diagnoses are commonly reported [5, 40]. Whilst it is tempting to attribute some of this high prevalence of pain to HIV infection, other causes may also be common – for example, among indigenous adults in San Francisco in the Research on Access to Care in the Homeless (REACH) study [41], physical assault and living conditions were commonly cited as causes of pain.

Whilst we did not aim to identify specific risk factors for current pain, pain was more commonly reported in women who, in our study, were also more likely to have acquired HIV infection through sex with men and to be of black African origin, and in those of lower educational attainment. Associations with gender in the published literature have been inconsistent [4,6,41], but lower educational levels have been reported to be associated with an increased prevalence of pain [41]. Older age is generally associated with an increased risk of pain as well as greater pain severity [5, 38, 39], consistent with our own findings. An

association of pain with more advanced HIV infection (as expressed by lower current/nadir CD4 counts, higher HIV viral loads and/or longer duration of HIV infection) has been reported previously [4, 5, 38].

Findings regarding other pain-related markers were somewhat less consistent. Whilst analgesic use was more common in older PLWH, joint problems occurred at a similar rate in both older groups in our study. Although a high proportion of participants had consulted a doctor about their pain (with no large differences between the two older groups in the study), visits to the GP for pain-related reasons were, if anything, more common in older HIV-negative controls, likely reflecting the fact that PLWH in the UK are under close management at their HIV clinic and are more likely to consult their HIV consultant for issues relating to pain than they are to consult a GP (HIV care in the UK is generally provided by hospital specialists). Other studies have reported high rates of healthcare resource use due to pain [5, 39, 42]. In a study of 103 people with HIV-related neuropathic pain [42], participants had been prescribed an average of 0.7 non-prescription pain-related medications (antiepileptics and opioids being most common) over the past 4 weeks with around 20% having received 3 or more such medications. Among primary care attendees in New York City [39], those reporting chronic pain had more emergency department visits and more radiology procedures with a trend towards a greater number of inpatient admissions. These studies did not generally make comparisons to a similar HIV-negative control group, and therefore it is unclear whether pain-related resource use in PLWH is any higher than would be expected in a similarly aged group in the general population. In one study of veterans with and without HIV in the United States [43], 13% of participants reported nonmedical use of prescription opioids, although in adjusted analyses no association was reported with HIV status.

Whilst only a small proportion of participants reported missing days of work or study due to pain, those with pain were less likely to be in full-time work and more likely to be unemployed or off sick than those without pain. An impact on work has been reported in other studies: Mann reported that among those with neuropathic pain, there was a 36.1% overall work impairment due to the pain which increased with increasing pain severity [42]. Total unadjusted annualized costs due to HIV-related neuropathic pain ranged from $9,900 to $25,822 per person, depending on the severity of the pain.

Among PLWH, we noted strong associations between the presence of pain and depressive symptoms, quality-of-life and functional impairment, regardless of age, as reported in other studies [5, 8, 42, 44]. Merlin [17] reported that current pain was associated with impairments in mobility, self-care and usual activities. A causal association between pain and interference with daily activities is supported by findings from a randomised trial of a pain education intervention, in which those randomised to the intervention experienced reduced pain interference with daily activities after an 8-week period [45]. Associations with substance use have also been reported [8, 38, 39], with pain serving both as a mediator and as a predictor of more use of recreational drugs, as well as more depressive symptoms [46]. Other negative effects of pain include direct associations with reduced social support [26] and with higher rates of unprotected vaginal or anal sex [29], raising concern that pain in PLWH may also lead to worse outcomes on ART. Whilst we were unable to consider this association in our cross-sectional analysis (the majority of POPPY participants were on stable ART at recruitment), Surratt [7] reported that those with untreated pain had a 42% lower odds of 95% medication adherence in the previous week compared to those who were pain-free.

As yet, the mechanisms by which HIV may lead to an increased risk of pain remain unclear. In 2013, Merlin [47] proposed a conceptual biopsychosocial framework for understanding chronic pain in PLWH, which includes biological (such as HIV neuropathy), psychological (following traumatic events) and social (environmental and relationship) factors. More recently [48], Merlin noted significantly higher levels of IL-1β a marker already implicated in a range of inflammatory and autoimmune diseases, in PLWH with chronic pain than in those without chronic pain, suggesting a biological pathway. Thus, interventions to reduce the burden of pain in this population need to address both physical and psychological factors. Whilst there is some evidence to suggest that self-management interventions may be effective in improving pain and physical symptoms, the quality of evidence to support these interventions is relatively poor [49]. A recent pilot study [50] has, however, demonstrated feasibility and acceptability of such an approach.

The large sample of PLWH in our study is broadly representative of older PLWH in western European settings, where the population is optimally treated for their HIV (with high levels of viral suppression). This has allowed us to describe the prevalence of pain among PLWH in an era of very effective treatment. In comparison to many earlier studies, our study also benefits from the inclusion of appropriately selected HIV-negative controls with similar

characteristics to the older PLWH in the study, allowing us to determine the role of HIV infection in the development of pain. Indeed, our study also reports a high prevalence of pain in older HIV-negative people from a similar demographic background and with similar lifestyles – thus, the contribution of HIV itself to the high reported rate of pain in PLWH may be less than widely thought, with other contributory causes being common in this age group. However, some limitations must be noted. Firstly, whilst the POPPY study is a prospective cohort, the analyses reported herein relate to the baseline visit only limiting inferences around causality - future analyses of the longitudinal follow-up of this cohort will permit more detailed analyses of the impact of pain on longer-term general and health-related outcomes as well as the identification of predictors (both HIV-related and HIV-unrelated) of incident and chronic pain. Due to the observational nature of the study, we cannot rule out the possibility that unmeasured common causes of pain and negative health outcomes may exist, which may introduce confounding. Whilst our cohort is broadly representative of the older population of PLWH in the UK and Ireland, the fact that most participants are engaged in care and are on stable ART may have introduced some selection bias; equally, this population may represent a cohort that has 'survived' through earlier eras of ART and may not be representative of those who are infected with HIV in more recent years.

Conclusions

Our study confirms that even in the era of effective ART, and in individuals with largely controlled HIV infection, pain remains common among PLWH with major impact on quality-of-life and associated healthcare and societal costs. Interventions are required to assist clinicians to proactively manage pain in their patients, and to assist PLWH to communicate their pain to clinicians and to self-manage pain and related symptoms. Our findings support the need for routine assessment of pain in this group. Further longitudinal studies of the severity, location and contributors to pain in PLWH will support the development of effective, low cost and easy to manage interventions for pain management.

References

1. May MT, Gompels M, Delpech V, Porter K, Orkin C, Kegg S*, et al.* **Impact on life expectancy of HIV-1 positive individuals of CD4+ cell count and viral load response to antiretroviral therapy.** *AIDS* 2014; **28**: 1193-1202.
2. Marcus JL, Chao CR, Leyden WA, Xu L, Quesenberry CP, Klein DB*, et al.* **Narrowing the gap in life expectancy between HIV-infected and HIV-uninfected individuals with access to care.** *J Acquir Imm Defic Syndr* 2016; **73**: 39-46.
3. Smit M, Brinkman K, Geerlings S, Smit C, Thyagarajan K, Sighem Av, *et al.* **Future challenges for clinical care of an ageing population infected with HIV: a modelling study.** *Lancet Infect Dis* 2015; **15**: 810-818.
4. da Silva JG, Anaximandro da Rocha Morgan, Cavalcante Monteiro Melo F, Kelly dos Santos I, Morais de Azavado KP, Jefferson de Medeiros H*, et al.* **Level of pain and quality of life of people living with HIV/AIDS pain and quality of life in HIV/AIDS.** *AIDS Care* 2017; **29**: 1041-1048.
5. Lawson E, Sabin C, Perry N, Richardson D, Gilleece Y, Churchill D*, et al.* **Is HIV painful? An epidemiological study of the prevalence and risk factors for pain in HIV-infected patients.** *Clin J Pain* 2015; **31**: 813-819.
6. Parker R, Stein DJ, Jelsma J. **Pain in people living with HIV/AIDS: a systematic review.** *J Int AIDS Soc* 2014; 17: 18719.
7. Surratt HL, Kurtz SP, Levi-Minzi MA, Cicero TJ, Tsuyuki K, O'Grady CL. **Pain treatment and antiretroviral medication adherence among vulnerable HIV-positive patients.** *AIDS Pat Care & STDs* 2015; **29**: 186-192.
8. Merlin JS, Cen L, Praestgaard A, Turner M, Obando A, Alpert C, *et al.* **Pain and physical and psychological symptoms in ambulatory HIV patients in the current treatment era.** *J Pain Symptom Manage* 2012; **43**: 638-645.
9. Evans SR, Ellis RJ, Chen H, Yeh T-M, Lee AJ, Schifitto G, *et al*. **Peripheral neuropathy in HIV: prevalence and risk factors.** *AIDS* 2011; **25**: 919-928.
10. Chen H, Clifford DB, Deng L, Wu K, Lee AJ, Bosch RJ*, et al.* **Peripheral neuropathy in ART-experienced patients: prevalence and risk factors.** *J Neurovirol* 2013; **19**: 557-564.
11. Cherry CL, Wadley AL, Kamerman PR. **Diagnosing and treating HIV-associated sensory neuropathy: a global perspective**. *Pain Manage* 2016; **6:** 191-199.

12. Dotan I, Reisenberg K, Toledano R, Schlaeffer A, Smolyakov A, Saidel-Odes L, *et al.* **Prevalence and characteristics of fibromyalgia among HIV-positive patients in southern Israel.** *Clin Exp Rheumatol* 2016; **34(2 Suppl 96)**: S34-S39.
13. Lagana L, Chen X-H, Koopman C, Classen C, Kimerling R, Spiegel D. **Depressive symptomatology in relation to emotional control and chronic pain in persons who are HIV positive**. *Rehabilitation Psychology* 2002; **47**: 402-414.
14. Rosenfeld B, Breitbart W, McDonald MV, Passik SD, Thaler H, Portenoy RK. **Pain in ambulatory AIDS patients. II: Impact of pain on psychological functioning and quality of life.** *Pain* 1996; **68**: 323-328.
15. Simms VM, Higginson IJ, Harding R. **What palliative care-related problems do patients experience at HIV diagnosis? A systematic review of the evidence.** *J Pain Symptom Manage* 2011; **42**: 734-753.
16. Sherr L, Lampe F, Fisher M, Arthur G, Anderson J, Zetler S, *et al*. **Suicidal ideation in UK HIV clinic attenders**. *AIDS* 2008; **22**: 1651-1658.
17. Merlin JS, Westfall AO, Chamot E, Overton ET, Willig JH, Ritchie C, *et al.* **Pain is independently associated with impaired physical function in HIV-infected patients.** *Pain Med* 2013; **141**: 1985-1993.
18. Harding R, Clucas C, Lampe FC, Leake Date H, Fisher M, Johnson M, *et al.* **What factors are associated with patient self-reported health status among HIV outpatients? A multi-centre UK study of biomedical and psychosocial factors.** *AIDS Care* 2012; **24**: 963-971.
19. de Sola H, Salazar A, Duenas M, Ojeda B, Failde I. **Nationwide cross-sectional study of the impact of chronic pain on an individual's employment: relationship with the family and the social support.** *BMJ Open* 2016; **6:** p. e012246.
20. Harding R, Lampe FC, Norwood S, Date HL, Clucas C, Fisher M*, et al.* **Symptoms are highly prevalent among HIV outpatients and associated with poor adherence and unprotected sexual intercourse.** *Sex Transm Infect* 2010: **86**: 520-524.
21. Sherr L, Lampe F, Norwood S, Leake Date H, Harding R, Johnson M, *et al*. **Adherence to antiretroviral treatment in patients with HIV in the UK: a study of complexity.** *AIDS Care* 2008; **20**: 442-448.
22. Lampe FC, Harding R, Smith CJ, Phillips AN, Johnson M, Sherr L**. Physical and psychological symptoms and risk of virologic rebound among patients with virologic suppression on antiretroviral therapy.** *J Acquir Immune Defic Syndr* 2010; **54**: 500-505.

23. Clucas C, Harding R, Lampe FC, Anderson J, Date HL, Johnson M, *et al*. **Doctor-patient concordance during HIV treatment switching decision-making.** *HIV Med* 2011; **12**: 87-96.
24. Sherr L, Lampe F, Norwood S, Leake-Date H, Fisher M, Edwards S, *et al*. **Successive switching of antiretroviral therapy is associated with high psychological and physical burden.** *Int J STD & AIDS* 2007; **18**: 700-704.
25. Safo SA, Blank AE, Cunningham CO, Quinlivan EB, Lincoln T, Blackstock OJ**. Pain is associated with missed clinic visits among HIV-positive women.** *AIDS Behav* 2017; **21**: 1782-1790.
26. Mitchell MM, Maragh-Bass AC, Nguyen TQ, Isenberg S, Knowlton AR. **The role of chronic pain and current substance use in predicting negative social support among disadvantaged persons living with HIV/AIDS.** *AIDS Care* 2016; **28**: 1280-1286.
27. The Antiretroviral Therapy Cohort Collaboration. **Mortality of HIV-infected patients starting potent antiretroviral therapy: comparison with the general population in nine industrialized countries.** *Int J Epidemiol* 2009; **38**: 1624-1633.
28. Peltzer K. **HIV-related symptoms and management in HIV and antiretroviral therapy patients in KwaZulu-Natal, South Africa: A longitudinal study.** *SAHARA-J: Journal of Social Aspects of HIV/AIDS* 2013; **10**: 96-104.
29. Tsui JI, Cheng DM, Coleman SM, Blokhina E, Gnatienko N, Bryant K, *et al*. **Pain and risk behaviors among HIV-Infected persons in St. Petersburg, Russia.** *AIDS Behav* 2017; **21**: 1775-1781.
30. Harding R, Clucas C, Lampe FC, Norwood S, Leake Date H, Fisher M*, et al***. Behavioral Surveillance Study: Sexual risk taking behaviour in UK HIV outpatient attendees.** *AIDS Behav* 2012; **16**: 1708-1715.
31. Bagkeris E, Burgess L, Mallon PW, Post FA, Boffito M, Sachikonye M, *et al*. **Cohort profile: the Pharmacokinetic and clinical Observations in PeoPle over fiftY (POPPY) Study.** *Int J Epidemiol* 2018; in press.
32. UK CHIC Study Steering Committee. **The creation of a large UK-based multicentre cohort of HIV-infected individuals: The UK Collaborative HIV Cohort (UK CHIC) Study.** *HIV Med* 2004; **5:** 115-124.
33. McGettrick P, Ghavami-Kia B, Tinago W, Macken A, O'Halloran J, Lambert JS, *et al*. **The HIV Care Cascade and sub-analysis of those linked to but not retained in care:**

the experience from a tertiary HIV referral service in Dublin Ireland. *HIV Clin Trials* 2017: **18**: 93-95.

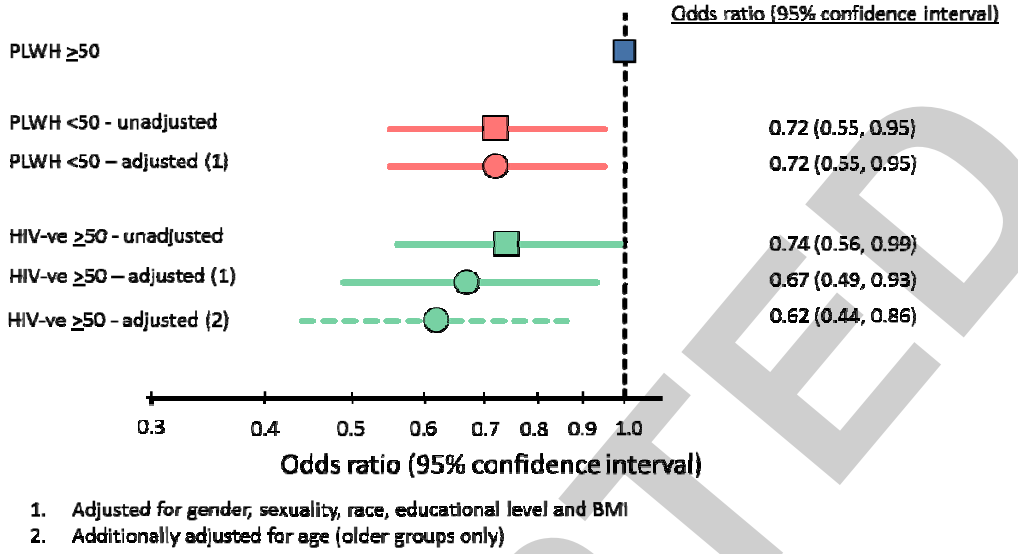
34. Ware JE, Kosinski M, Keller SD. SF-36 Physical and Mental Health Summary Scales: A User's Manual, 2nd ed. Boston, MA, Health Assessment Lab, 1994.
35. Radloff L**. The CES-D scale: a self-report depression scale for research in the general population.** *Appl Psychol Meas* 1977; **1:** 385-401.
36. Kroenke K, Spitzer RL, Williams JB. **The PHQ-9: validity of a brief depression severity measure**. *J Gen Intern Med* 2001; **16**: 606-613.
37. Lawton MP, Brody EM. **Assessment of older people: self-maintaining and instrumental activities of daily living.** *Gerontologist* 1969; **9**: 169-173.
38. Richardson JL, Heikes B, Karim R, Weber K, Anastos K, Young M. **Experience of pain among women with advanced HIV disease.** *AIDS Pat Car & STDs* 2009; **23**: 503-511.
39. Jiao JM, Jebakumar J, George MC, Simpson DM, Robinson-Papp J**. Chronic pain disorders in HIV primary care: clinical characteristics and association with healthcare utilization.** *Pain* 2016; **157**: 931-937.
40. Wilson NL, Azuero A, Vance DE, Richman JS, Moneyham LD, Raper JL, *et al*. **Identifying symptom patterns in people living with HIV disease.** *J Assoc Nurses AIDS Care* 2016; **27**: 121-132.
41. Miaskowski C, Penko JM, Guzman D, Mattson JE, Bangsberg DR, Kushel MB. **Occurrence and characteristics of chronic pain in a community-based cohort of indigent adults living with HIV infection.** *J Pain* 2011; **12**: 1004-1016.
42. Barry DT, Goulet JL, Kerns RK, BeckerWC, Gordon AJ, Justice AC, *et al.* **Nonmedical use of prescription opioids and pain in veterans with and without HIV.** *Pain* 2011; **152:** 1133-1138.
43. Mann R, Sadosky A, Schaefer C, Baik R, Parsons B, Nieshoff E*, et al*. **Burden of HIV-related neuropathic pain in the United States.** *J Int Associ Providers of AIDS Care* 2016; **15**: 114-125.
44. Uebelacker LA, Weisberg RB, Herman DS, Bailey GL, Pinkston-Camp MM, Stein MD. **Chronic pain in HIV-infected patients: relationship to depression, substance use, and mental health and pain treatment.** *Pain Med* 2015; **16**: 1870-1881.
45. 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: a randomized controlled trial. *J Pain Symp Management* 2015; **50**: 80-90.

46. Tsao JCI, Stein JA, Ostrow D, Stall RD, Plankey MW. **The mediating role of pain in substance use and depressive symptoms among Multicenter AIDS Cohort Study (MACS) participants.** *Pain* 2011; **152**: 2757-2764.
47. Merlin JS, Zinski A, Norton WE, Ritchie CS, Saag MS, Mugavero MJ, *et al*. **A conceptual framework for understanding chronic pain in patients with HIV.** *Pain Practice*. 2013; **14**: 207-216.
48. Merlin JS, Westfall AO, Heath SL, Goodin BR, Stewart JC, Sorge RE, *et al*. **IL-1 levels are associated with chronic multisite pain in people living with HIV.** *J Acquir Immune Defic Syndr* 2017; **75**: e99-e103.
49. Nkhoma K, Norton C, Sabin C, Winston A, Merlin J, Harding R. **Self-management interventions for pain and physical symptoms among people living with HIV: a systematic review of the evidence.** *J Acquir Immune Defic Syndr* 2018 (in press).
50. Merlin JS, Westfall AO, Long D, Davies S, Saag M, Demonte W, *et al*. **A randomized pilot trial of a novel behavioural intervention for chronic pain tailored to individuals with HIV.** *AIDS Behav* 2018; 2018 doi.org/10.1007/s10461-018-2028-2.

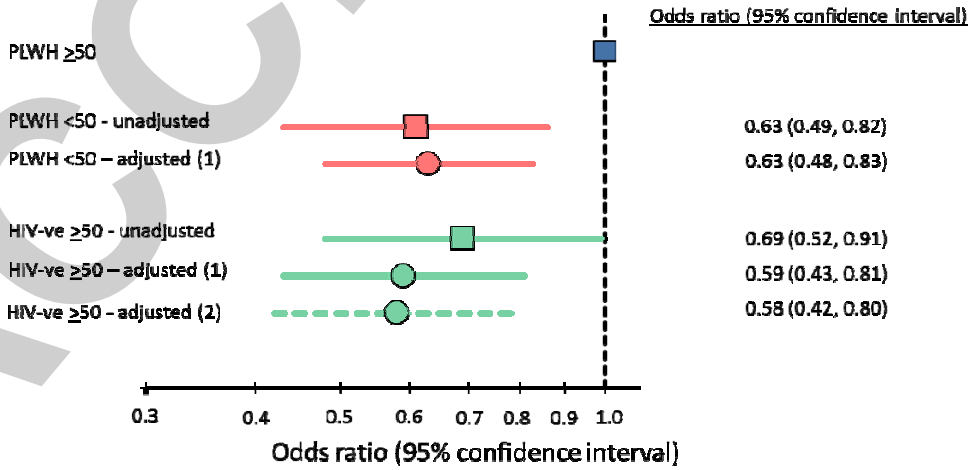
Figure 1: Results from univariate and multivariable analyses to identify predictors of a) any aches or pains in the past month and b) current pain

a) Any aches or pains in the past month



1. Adjusted for gender, sexuality, race, educational level and BMI
2. Additionally adjusted for age (older groups only)

b) Current pain



1. Adjusted for gender, sexuality, race, educational level and BMI
2. Additionally adjusted for age (older groups only)

Table 1: Characteristics of a) all POPPY participants included in the analysis of pain data, b) those who do and do not report pain in the last month, and c) those who do and do not report current pain; table entries show n and column percentages, unless otherwise stated

		Total with pain data	Aches or pains in the last month		P-value*	Current pain		P-value*
			Yes	No		Yes	No	
Number of participants		1325 (100.0)	882	443		580	745	
Cohort	Older HIV-positive	676 (51.0)	473 (53.6)	203 (45.8)		330 (56.9)	346 (46.4)	
	Younger HIV-positive	357 (26.9)	224 (25.4)	133 (30.0)		134 (23.1)	223 (29.9)	
	Older HIV-negative	292 (22.0)	188 (21.0)	107 (24.2)	0.03	116 (20.0)	176 (23.6)	0.0007
Gender	Male	1075 (81.1)	698 (79.1)	377 (85.1)		455 (78.5)	620 (83.2)	
	Female	250 (18.9)	184 (20.9)	66 (14.9)	0.01	125 (21.6)	125 (16.8)	0.03
Sexuality/risk group	MSM	935 (70.6)	603 (68.4)	332 (74.9)		397 (68.5)	538 (72.2)	
	Heterosexual	390 (29.4)	279 (31.6)	111 (25.1)	0.02	183 (31.6)	207 (27.8)	0.15
Race	White	1141 (86.1)	744 (84.4)	397 (89.6)		490 (84.5)	651 (87.4)	
	Black African	184 (13.9)	138 (15.7)	46 (10.4)	0.01	90 (15.5)	94 (12.6)	0.15
Education	O levels or lower	341 (25.7)	253 (28.7)	88 (19.9)		177 (30.5)	164 (22.0)	
	A levels	193 (14.6)	122 (13.8)	71 (16.0)		77 (13.3)	116 (15.6)	
	Higher than A levels/unknown	791 (59.7)	507 (57.5)	284 (64.1)	0.002	326 (56.2)	405 (62.4)	0.002
Age (years)	Median (IQR)	54 (49, 60)	54 (49, 60)	53 (48, 59)	0.01	55 (50, 60)	53 (48, 59)	0.0005
BMI (kg/m^2)	Median (IQR)	25.7 (23.3, 28.6)	25.9 (23.3, 28.9)	25.4 (23.3, 28.0)	0.07	26.0 (23.6, 29.1)	25.4 (23.1, 28.2)	0.0009
Year of baseline visit	2013	187 (14.1)	116 (13.2)	71 (16.0)		78 (13.5)	109 (14.3)	
	2014	587 (44.3)	406 (46.0)	181 (40.9)		283 (48.8)	304 (40.8)	
	2015	497 (37.5)	324 (36.7)	173 (39.1)		197 (34.0)	300 (40.3)	
	2016	54 (4.1)	36 (4.1)	18 (4.1)	0.27	22 (3.8)	32 (4.3)	0.03
HIV-positive cohorts only								
Current CD4 (cells/mm^3)	Median (IQR)	626 (478, 810)	630 (477, 816)	607 (479, 806)	0.49	624 (473, 809)	626 (479, 810)	0.94
Nadir CD4 (cells/mm^3)	Median (IQR)	203 (102, 306)	200 (87, 300)	218 (128, 332)	0.004	185 (85, 290)	217 (120, 324)	0.0009
On antiretroviral therapy		1011 (97.9)	682 (97.9)	329 (97.9)	1.00	456 (98.3)	555 (97.5)	0.55
Viral load ≤50 copies/ml		925 (89.9)	629 (90.6)	296 (88.4)	0.31	424 (92.0)	501 (88.2)	0.06

* P-value obtained from Chi-squared test (categorical covariates) or Mann-Whitney U test (continuous covariates)

MSM: men who have sex with men; IQR: interquartile range.

Table 2: Other markers of pain assessed as part of the baseline POPPY study visit, stratified by study group

	Overall	Group			p-value (Chi-squared test)
		Older HIV-positive	Younger HIV-positive	Older HIV-negative	
Number of participants	1377	699	374	304	
Concomitant medication					
Any reported analgesic use	210 (15.3)	130 (18.6)	49 (13.1)	31 (10.2)	0.001
Reported health problems					
Any joint problem	629 (45.7)	371 (53.1)	108 (28.9)	150 (49.3)	0.0001
Resource use					
GP – generalised pain	22 (1.6)	10 (1.4)	7 (1.9)	5 (1.6)	0.86
GP – back pain	65 (4.7)	28 (4.0)	16 (4.3)	21 (6.9)	0.12
GP – joint pain problems	104 (7.6)	50 (7.2)	21 (5.6)	33 (10.9)	0.03
GP – other pain	112 (8.1)	58 (8.3)	27 (7.2)	27 (8.9)	0.71
Any GP visit for pain-related reasons	264 (19.2)	128 (18.3)	59 (15.8)	77 (25.3)	0.005
Any GP visits	1052 (76.4)	547 (78.3)	260 (69.5)	245 (80.6)	0.0009
Median (range) number of GP visits	2 (1-32)	2 (1-32)	2 (1-23)	2 (1-20)	0.09
Other specialist – pain management	19 (1.4)	14 (2.0)	2 (0.5)	3 (1.0)	0.12
Any pain-related resource use	274 (19.9)	136 (19.5)	59 (15.8)	79 (26.0)	0.004

Table 3: Association between current pain, depression scores (CES-D, PHQ9) and components of quality-of-life (SF-36) among PLWH, stratified by age group

	PLWH aged >50 years		p-value[2]	PLWH aged <50 years		p-value[2]
	No current pain	Current pain		No current pain	Current pain	
Depressive symptoms[1]						
CES-D score, median (IQR)	9 (3, 17)	15 (7, 26)	0.0001	7 (3, 15)	14 (7, 27)	0.0001
Significant depression (≥16), n (%)	92 (28.5)	148 (50.0)	0.0001	51 (24.6)	57 (46.3)	0.0001
PHQ-9 score, median (IQR)	2 (0, 7)	7 (2, 12)	0.0001	3 (1, 7)	6 (2, 13)	0.0001
Current depression (≥5), n (%)	120 (36.6)	183 (60.2)	0.0001	85 (39.9)	73 (57.5)	0.002
Quality of life (SF-36 subscales)[1], median (IQR)						
Physical functioning	90 (75, 100)	72 (45, 90)	0.0001	100 (95, 100)	90 (55, 100)	0.0001
Role limitations due to physical health	100 (50, 100)	50 (0, 100)	0.0001	100 (100, 100)	75 (0, 100)	0.0001
Role limitations due to emotional problems	100 (33, 100)	83 (0, 100)	0.0002	100 (66, 100)	67 (0, 100)	0.0001
Energy/fatigue	65 (50, 80)	50 (25, 65)	0.0001	65 (50, 80)	50 (30, 65)	0.0001
Emotional well-being	80 (60, 88)	68 (52, 84)	0.0001	80 (60, 88)	68 (52, 84)	0.001
Social functioning	90 (65, 100)	67 (42, 90)	0.0001	90 (67, 100)	67 (42, 90)	0.0001
General health	70 (55, 80)	50 (30, 70)	0.0001	75 (55, 85)	60 (40, 75)	0.0001
Lawton Instrumental Activities of Daily Living						
Fully functioning, n (%)	302 (91.0)	241 (76.5)	0.0001	205 (95.4)	98 (77.2)	0.0001

[1]For CES-D and PHQ-9, higher values indicate greater depressive symptoms; for the sub-scales of the SF-36, lower values indicate poorer quality of life. [2]p-values obtained from Mann-Whitney U test (numerical outcomes) or Chi-squared test (categorical outcomes)