Pain Medicine 2017; 18: 2289–2295
doi: 10.1093/pm/pnx057

OXFORD

Preliminary Research Article

Detectable Viral Load May Be Associated with Increased Pain Sensitivity in Persons Living with HIV: Preliminary Findings

Burel R. Goodin, PhD,*,† Michael A. Owens, BS, BA,* Lindsey R. Yessick, BS,* Rachael L. Rainey,* Jennifer I. Okunbor,* Dyan M. White, BS,* Kaneisha A. Mushatt,* Olivia A. Harmon,* Sonya L. Heath, MD,‡‡ and Jessica S. Merlin, MD‡‡,§

*Department of Psychology, †Division of Pain Medicine, ‡‡Division of Infectious Diseases, and §Division of Gerontology, Geriatrics, and Palliative Care, University of Alabama at Birmingham (UAB), Birmingham, Alabama, USA

Correspondence to: Burel R. Goodin, PhD, University of Alabama at Birmingham, 1300 University Boulevard, Campbell Hall, Room 328, Birmingham, AL 35294, USA. Tel: 205-934-8743; Fax: 205-975-6110; E-mail: bgoodin1@uab.edu.

Funding sources: This research was supported by the Creative and Novel Ideas in HIV Research (CNIHR) Program (BRG) through a supplement to the University of Alabama at Birmingham (UAB) Center for AIDS Research funding (P30 AI027767). This funding was made possible by collaborative efforts of the Office of AIDS Research, the National Institute of Allergy and Infectious Diseases, and the International AIDS Society. This research was also supported by the National Institutes of Health (K23MH104073, JSM).

Conflicts of interest: The authors have no conflicts of interest to report.

Abstract

Objective. Animal models have previously shown that HIV is associated with hyperalgesia, or heightened sensitivity to painful stimuli. Efforts to determine whether this finding translates to humans are presently lacking. Among persons living with HIV (PLWH), those with detectable viral loads may be at greatest risk for heightened pain sensitivity. It was hypothesized that PLWH with detectable viral loads would be more sensitive to painful stimuli compared with PLWH without detectable viral loads and healthy controls without HIV.

Design. A total of 47 PLWH and 50 community-dwelling, healthy adults without HIV (controls) were recruited. Participants completed a quantitative sensory testing protocol to assess threshold, tolerance, and temporal summation in response to painful mechanical and heat stimuli. Most recent viral load was collected from medical records, and viral load was considered detectable if the count was greater than 50 copies/mL of blood. Of the 47 PLWH, 11 (23.4%) had detectable viral loads, the median viral load count was 10,200 copies/mL.

Results. PLWH with detectable viral loads demonstrated significantly lower pain thresholds for mechanical stimuli ($F_{2,89} = 3.15$, $P = 0.049$), significantly lower heat pain tolerances ($F_{2,89} = 3.38$, $P = 0.039$), and significantly greater temporal summation of heat pain at 48 °C ($F_{2,89} = 10.66$, $P < 0.001$) and 50 °C ($F_{2,89} = 3.82$, $P = 0.026$), compared with PLWH without detectable viral loads and healthy controls.

Conclusions. These preliminary results tentatively suggest that the detectable presence of the virus may sensitize PLWH to painful mechanical and heat stimuli.

Key Words. Human immunodeficiency virus (HIV); viral load; pain sensitivity

Introduction

In the current antiretroviral treatment era, persons living with HIV (PLWH) can achieve a near-normal life expectancy. However, they experience a high burden of co-morbidity, including chronic pain. The estimates of chronic pain prevalence among PLWH range from 39% to 85%, which is higher than reported in the general population [1–3]. In addition to the classically described

syndrome of HIV neuropathy, non-neuropathic pain including regional musculoskeletal pain syndromes and chronic multisite pain is common [4]. One possible explanation for increased pain in PLWH is that HIV infection is associated with greater sensitivity to painful stimuli. This possibility has yet to be directly tested in humans. Research on this topic is important because heightened pain sensitivity is a risk factor for the development of chronic pain [5].

Animal studies suggest that envelope proteins such as GP120, found on the surface of HIV, activate astrocytes and microglia in the central nervous system [6,7]. In turn, these GP120-activated astrocytes and microglia facilitate the endogenous processing of painful stimuli, thus leading to heightened pain sensitivity [7]. For instance, mechanical allodynia and heat hyperalgesia have been observed in rodents following intrathecal injection of GP120 [8]. Given the increased presence of GP120 due to circulating virus, we hypothesized that PLWH with detectable viral loads would have heightened pain sensitivity compared with those who are virologically suppressed (the biologic treatment end point of antiretroviral therapy).

Our goal was to test this hypothesis in a preliminary fashion by examining differences in pain sensitivity (i.e., threshold, tolerance, temporal summation of pain) between PLWH with and without detectable viral loads as well as a group of healthy controls without HIV. To be consistent with previous animal research [8], we specifically investigated sensitivity to mechanical and heat stimuli. This study represents an important first step toward determining whether PLWH with detectable viral loads tend to have heightened pain sensitivity, a purported risk factor for the development of chronic pain.

Methods

Procedures and Participants

A total of 47 PLWH without chronic pain were recruited from a large, urban HIV clinic in the Southeast that provides comprehensive medical, behavioral, and social services to adults with HIV. Fifty community-dwelling, healthy control participants without chronic pain were also recruited from local libraries and low-income community shelters via posted fliers. Only healthy controls without HIV (by self-report) were included. Study procedures were approved by our Institutional Review Board and carried out in accordance with guidelines for the ethical conduct of research. Written informed consent was obtained from each participant prior to the study, and they were compensated for their involvement.

Sociodemographic information was collected from all participants and included age, sex, and racial background, as well as educational attainment and poverty status. Annual household income adjusted for number of occupants was used to determine poverty status according to 2016 guidelines put forth by the US Department of Health and Human Services [9]. Further, depressive symptoms [10] and pain catastrophizing [11] can be potent predictors of pain sensitivity; therefore, information regarding these psychological processes was collected and included in data analysis as statistical controls. Pain sensitivity was objectively evaluated using a quantitative sensory testing protocol that included noxious mechanical and heat stimuli.

For PLWH, medical record review was completed to determine whether any participants were actively being prescribed medications that could affect their pain sensitivity, such as selective serotonin reuptake inhibitors (SSRIs)/serotonin-norepinephrine reuptake inhibitors (SNRIs) or neuroleptics. Medical records were also used to determine most recent CD4+ T-cell count, a measure of immune status, and most recent viral load value. Most recent CD4+ and viral load counts were obtained within 12 months of study participation for all PLWH. Mean number of days between most recent viral load assessment and study participation was 93.2 days (SD = 87.3 days) and ranged from two days to 363 days. Those PLWH with 50 or more copies of virus/mL were considered to have a detectable viral load; all others were considered virologically suppressed (i.e., without detectable viral loads). This cutoff ($\geq$50) was selected due to its clinical relevance as an HIV treatment end point [12,13] and also because we hypothesized that even a small amount of detectable HIV virus in the blood may be sufficient to augment pain sensitivity. PLWH self-reported the date (month, year) when first diagnosed with HIV. This information was used to determine duration of HIV diagnosis (in months) by subtracting date of HIV diagnosis from date of study participation.

Measures

Center for Epidemiological Studies–Depression Scale

The Center for Epidemiological Studies–Depression Scale (CES-D) is a 20-item measure of depressive symptoms including negative mood, guilt/worthlessness, helplessness/hopelessness, psychomotor retardation, loss of appetite, and sleep disturbance [14]. The CES-D is generally accepted as a useful tool for screening depressive symptomatology. The CES-D total score is calculated by summing the 20-item responses. Higher scores on the CES-D are indicative of greater depressive symptoms.

Pain Catastrophizing Scale

The standard Pain Catastrophizing Scale (PCS) 54 is a 13-item scale that assesses catastrophic thinking in response to pain [15]. The standard PCS assesses catastrophic pain-related cognitive-emotional processes by asking participants to recall their experiences during a

past occurrence of pain. The PCS total score is calculated by summing the 13-item responses. Higher scores on the PCS are indicative of greater pain-related catastrophizing.

Quantitative Sensory Testing

Mechanical Sensitivity. To test mechanical pain sensitivity, we assessed pressure pain thresholds (PPTs) on the right distal third of the dorsal forearm and the ipsilateral trapezius. A digital algometer (Medoc, Ltd., AlgoMed, Ramat Yishai, Israel) was used to deliver noxious pressure (measured in kilopascals) stimulation via a handheld stainless steel probe with a circular, rubber-tipped contact surface of 1.0 cm^2 [16]. The algometer was applied three separate times at each anatomic location in counterbalanced fashion. Participants indicated when the increasing pressure stimulation first became painful (i.e., pain threshold). Results of the three pain threshold readings for each anatomic location were averaged to obtain forearm and trapezius PPTs.

Heat Sensitivity. Thermal stimulation procedures were completed to assess heat pain threshold (HPTh), heat pain tolerance (HPTo), and temporal summation (TS) of heat pain at 48 °C and 50 °C (i.e., pain sensitivity) using established protocols [17]. Heat pain sensitivity was assessed using a Medoc Pathway Neurosensory Analyzer (Medoc, Ltd., Ramat Yishai, Israel) with a 30×30 mm thermode. For HPTh, participants indicated when the sensation first became painful, and for HPTo they indicated when the painful sensation was no longer tolerable. Three trials for HPTh and three for HPTo were delivered to the dorsal and ventral aspects of the dominant forearm, respectively. The three individual trials were averaged together to create overall HPTh and HPTo indices.

For TS of heat pain, participants underwent two separate trials using thermal stimulus intensities of 48 °C and 50 °C as target temperatures with 32 °C as the interpulse temperature. For each TS trial, sequences of five consecutive heat pulses of one-second duration were delivered with interpulse intervals of 2.5 seconds. Participants were instructed to rate the intensity of pain produced by each heat pulse on a 0 to 100 numeric rating scale such that 0 = no pain and 100 = the most intense pain imaginable. TS of heat pain at 48 °C and 50 °C was calculated by subtracting the first pain rating from the fifth pain rating as this reflected the Δ change score for the greatest amount of TS obtained.

Data Analysis

Differences in participant characteristics were examined using analysis of variance (ANOVA) for continuously measured variables and chi-square for categorically measured variables. Pearson correlations were used to examine zero-order relationships. Differences in mechanical and heat pain sensitivity were examined using analysis of covariance (ANCOVA) with post hoc analyses for pairwise comparisons across the three study groups: 1) PLWH with detectable viral loads, 2) PLWH without detectable viral loads, and 3) healthy controls. Statistical adjustments for multiple comparisons and inflated family-wise error rates were employed. To accomplish this, we first categorized our dependent variables into separate "families" that included: 1) HPTh, 2) HPTo, 3) TS of heat pain at 48 °C, and 4) TS of heat pain at 50 °C. We then performed a Holm-Bonferroni procedure to obtain corrected *P* values [18]. There were no missing data for any of the study variables. All analyses were carried out using SPSS, version 23.

Results

Participant Characteristics

Participant characteristics are shown in Table 1. Medical records confirmed that all 47 PLWH were actively being prescribed antiretroviral therapy, while 15% were being prescribed an SSRI/SNRI and 8.5% were being prescribed a neuroleptic. Eleven PLWH (23.4%) had detectable viral loads. The median viral load for these individuals was 10,200 copies/mL with an interquartile range of 220 to 45,500. The difference in mean CD4+ between PLWH with and without detectable viral loads approached significance ($F_{1,45} = 3.95$, $P = 0.053$), such that PLWH with detectable viral loads had lower CD4. Time since HIV diagnosis (in months) did not significantly differ between those with and without detectable viral loads.

The mean age of the study sample was 47.8 years (SD = 11.3 years), and the sample was comprised of 46.4% women and 66% African Americans (the remaining 34% were Caucasians). Age and sex did not significantly differ across the three study groups. Among PLWH, irrespective of viral load detectability, a significantly greater proportion were African American compared with Caucasian ($\chi^2 = 9.63$, $P = 0.008$). Further, significantly greater proportions of PLWH had educational attainment of high school or less ($\chi^2 = 25.51$, $P < 0.001$) and were living below the poverty line ($\chi^2 = 34.16$, $P < 0.001$) compared with healthy controls, again, irrespective of viral load detectability.

Depressive symptoms did not significantly differ across groups ($F_{2,94} = 1.66$, $P = 0.197$). Conversely, pain catastrophizing was found to significantly differ ($F_{2,93} = 10.91$, $P < 0.001$). Specifically, PLWH without detectable viral loads catstrophized more about pain than healthy controls ($P < 0.001$). The pain catastrophizing of PLWH with detectable viral loads did not significantly differ from the other two groups.

Covariates

Participants' race (coded as 0 = African American, 1 = Caucasian), educational attainment (coded as 0 = high school degree or less, 1 = some college or more),

Table 1 Participant characteristics

Variable	Healthy controls (N = 50)	HIV without detectable viral load (N = 36)	HIV with detectable viral load (N = 11)	*P*
Age (SD), y	49.0 (12.1)	47.2 (10.7)	44.4 (8.9)	0.422
Sex, %				0.147
Male	44.0	63.9	63.6	
Female	56.0	36.1	36.4	
Race, %				0.008
African American	52.0	77.8	90.9	
Caucasian	48.0	22.2	9.1	
Educational attainment, %				<0.001
HS or less	36.0	83.3	90.9	
Some college or more	64.0	16.7	9.1	
Poverty status, %				<0.001
Below poverty line	24.0	80.6	90.9	
Above poverty line	76.0	19.4	9.1	
CES-D (SD)	13.5 (10.0)	16.7 (10.3)	11.4 (9.4)	0.197
PCS (SD)	8.9 (7.7)	18.1 (10.2)	11.5 (10.3)	<0.001
CD4 + (SD)	N/A	758.6 (466.2)	460.8 (300.1)	0.053
Duration of HIV diagnosis, mo	N/A	149.3 (111.8)	128.6 (72.1)	0.570

CES-D = Center for Epidemiological Studies–Depression Scale; HS = high school; PCS = Pain Catastrophizing Scale.

poverty status (coded as 0 = below poverty line, 1 = above poverty line), depressive symptoms, and pain catastrophizing were included as covariates in all analyses presented below. Participants' age, sex, SSRI/SNRI and neuroleptic use were not included as covariates in any analyses.

Mechanical Pressure Pain Threshold

As demonstrated in Table 2, there were significant group differences found for PPT assessed at the trapezius ($F_{2,89} = 3.15$, $P = 0.049$). PLWH with detectable viral loads demonstrated significantly lower PPT in comparision with healthy controls ($P = 0.019$), but not PLWH without detectable viral loads ($P = 0.152$). The PPT of PLWH without detectable viral loads was not significantly different from healthy controls. The signficant difference remained even after Holm-Bonferroni adjustment. There were no signficant group differnces found for PPT assessed at the forearm ($F_{2,89} = 0.82$, $P = 0.370$).

Heat Pain Threshold and Tolerance

There were no significant differences for HPTh across the three groups ($F_{2,89} = 0.81$, $P = 0.449$). However, results showed significant group differences for HPTo ($F_{2,89} = 3.38$, $P = 0.039$). Specifically, PLWH with detectable viral loads had signficantly lower HPTo compared with PLWH without detectable viral loads ($P = 0.035$) and healthy controls ($P = 0.012$). These differences remained significant after Holm-Bonferroni adjustment. The HPTo of PLWH without detectable viral loads did not significantly differ from that of healthy controls (Table 2).

Temporal Summation of Heat Pain at 48 °C and 50 °C

Results presented in Table 2 showed significant differences in TS of heat pain at 48 °C ($F_{2,89} = 10.66$, $P < 0.001$) and 50 °C ($F_{2,89} = 3.82$, $P = 0.026$) with Holm-Bonferroni adjustment. At 48 °C, PLWH with detectable viral loads demonstrated significantly greater TS of heat pain than PLWH without detectable viral loads ($P = 0.016$) and healthy controls ($P < 0.001$). Further, PLWH without detectable viral loads had significantly greater TS of heat pain than healthy controls ($P = 0.001$). At 50 °C, PLWH with detectable viral loads demonstrated significantly greater TS of heat pain than healthy controls ($P = 0.008$), but not PLWH without detectable viral loads ($P = 0.11$). PLWH without detectable viral loads also had significantly greater TS of heat pain than healthy controls ($P = 0.024$).

Discussion

To our knowledge, this is the first study to test the hypothesis that detectable levels of HIV are associated with heightened pain sensitivity. Our preliminary findings suggest that PLWH with detectable viral loads may possess increased senstivity to painful mechanical and heat stimuli when compared with PLWH without detectable viral loads and healthy controls. In the case of heat pain TS, PLWH without detectable viral loads were more

Table 2 Pain sensitivity outcomes

Variable	Healthy controls (N = 50)	HIV without detectable viral load (N = 36)	HIV with detectable viral load (N = 11)	*P*
PPT–forearm (SD)	404.3 (189.9)	359.2 (181.7)	316.6 (197.8)	0.370
PPT–trapezius (SD)	458.1 (242.7)	386.8 (247.0)	271.6 (143.3)	0.049
HPTh (SD)	44.6 (3.9)	44.1 (3.5)	42.0 (3.9)	0.449
HPTo (SD)	48.7 (2.0)	47.9 (1.6)	46.1 (2.5)	0.039
TS 48 °C (SD)	–4.9 (16.3)	9.6 (18.3)	24.5 (27.4)	<0.001
TS 50 °C (SD)	4.5 (15.6)	13.8 (21.8)	25.9 (28.3)	0.026

TS is a Δ change score representing the difference in 0–100 pain ratings following the first heat pulse and the fifth heat pulse. Pressure was measured in kiloPascals, while heat was measured in Celsius.
HPTh = heat pain threshold; HPTo = heat pain tolerance; PPT = pressure pain threshold; TS = temporal summation.

pain sensitive than healthy controls at 48 °C and 50 °C stimuli. Consistent with our hypothesis, PLWH with detectable viral loads consistently demontrated the greatest magnitude of mechanical and heat pain sensitivity, as shown in Table 2.

The detectable presence of HIV circulating in the blood may contribute to increased pain sensitivity by directly impacting the central nervous system. For example, in a recent translational study conducted by Yuan and colleagues, it was found that the presence of envelope protein GP120 was significantly greater in the spinal dorsal horns of PLWH with chronic pain when compared with PLWH without chronic pain [7]. In the same study, GP120 was injected intrathecally into mice and the resulting pathology was compared between these mice and PLWH with chronic pain. Results showed extensive similarities between mice and human pathologies, including comparable pain behaviors, peripheral neuropathy, glial reactivation, synapse degeneration, and aberrant activation of pain-related signaling pathways in the spinal dorsal horn. It will be important for future confirmatory research in humans to examine whether GP120 and/or other HIV surface proteins are indeed responsible for eliciting increased pain sensitivity.

Chronic pain is quite prevalent in HIV, and as such it will be important for future research to continue examining pain sensitivity in PLWH. This is because it has been shown, albeit not yet in HIV, that increased sensitivity to painful stimuli is predictive of chronic pain development as well as poor chronic pain outcomes including greater severity of clinical pain and decreased physical functioning [5]. It is possible that the heightened pain sensitivity observed in this study may be representative of central sensitization [19]. Central sensitization of afferent nociceptive pathways could be a potentially important determinant of neuropathic and non-neuropathic chronic pain in PLWH [20], and those with detectable viral loads may be at greatest risk given the impact of HIV on the central nervous system. If future research on this topic confirms our findings, this could have important implications for HIV clinical care. For example, recent HIV treatment guidelines recommend that all PLWH receive antiretroviral therapy as this has been shown to improve long-term outcomes including mortality [21]. However, recent studies have found that more than half of PLWH are not in care [22], and as many as one-third of PLWH who are in care are not virologically suppressed [23]. Given the high prevalence of chronic pain in PLWH, pain prevention and management could perhaps be used in the future as motivators for PLWH to initiate antiretroviral therapy.

The following limitations must be considered when interpreting the current study's preliminary findings. First, the number of PLWH with detectable viral loads included in this study is low (N = 11), which limits the ability to reliably generalize our results to broader populations of PLWH with detectable viral loads. It is noteworthy that the percentage of PLWH with detectable viral loads in this study (23.4%) is consistent with the published point prevalence of detectable viral loads commonly found in the clinic from which PLWH were recruited [24]. We did not specifically over-recruit PLWH with detectable viral loads due to the exploratory nature of this work; therefore, their numbers were appropriately small in our sample. Second, viral load was not assessed at the time of study participation, but rather as part of routine clinical care. In some instances, most recent viral load was evaluated multiple months prior to study participation. Therefore, we cannot confirm the accuracy of viral loads in this study as some PLWH with detectable viral loads may have experienced improved viral suppression with treatment leading up to study participation. Third, we did not collect data related to viremia copy-years, a measure of cumulative HIV burden. This study incorporated a cross-sectional viral load measure, which fails to capture longitudinal exposure to HIV replication. It has been suggested that measurement of cumulative viral load burden over time (i.e., viremia copy-years) is important for understanding morbidity and mortality among PLWH in the modern treatment era [25]. This may also hold true for understanding chronic pain development in PLWH. Fourth, information pertaining to the different classes of

antiretroviral therapy (ART) being prescribed to the PLWH in this study was not systematically collected (e.g., protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors). Although ART regimens in the current HIV treatment era are much less toxic than in the past, it may be important for future research to examine whether type of ART regimen is associated with pain sensitivity in PLWH. Fifth, we were unable to ascertain ART exposure histories for PLWH or how long PLWH in this study had been using their current ART regimen. This information could be important for future HIV and pain sensitivity research to consider given that, in the past, use of dideoxynucleoside reverse transcription inhibitors has been associated with painful antiretroviral toxic neuropathy [26] and initiation of an ART regimen in ART-naïve PLWH has also been associated with onset of neuropathy for approximately the first year following initiation [27]. Lastly, healthy controls were asked to self-report their negative HIV status. However, we did not confirm this with blood tests.

Despite these limitations, our preliminary findings suggest that the detectable presence of HIV may be associated with increased mechanical and heat pain sensitivity. Although individuals with HIV appear to be at increased risk for chronic pain, the factors that contribute to its development and severity remain poorly understood. This pilot study is significant because it represents an initial step toward addressing this very knowledge gap. Further research is needed to replicate and expand the current study's findings, as well as to investigate the relationship between heightened pain sensitivity and the development of chronic pain in PLWH. It would also be worthwhile for future research to consider the various ways in which PLWH with detectable viral loads are likely to differ from those whose HIV is well controlled. For instance, some PLWH with detectable viral loads may be poorly adherent to their antiretroviral therapy regimens for reasons including social instability, burden of psychiatric disease, substance abuse, and other comorbid medical illness. Any or all of these factors could account, at least in part, for the heightened pain sensitivity observed among PLWH with detectable viral loads in this study.

References

1 Cervia LD, McGowan JP, Weseley AJ. Clinical and demographic variables related to pain in HIV-infected individuals treated with effective, combination antiretroviral therapy (cART). Pain Med 2010;11(4):498–503.

2 Merlin JS, Westfall AO, Chamot E, et al. Pain is independently associated with impaired physical function in HIV-infected patients. Pain Med 2013;14(12):1985–93.

3 Miaskowski C, Penko JM, Guzman D, et al. Occurrence and characteristics of chronic pain in a community-based cohort of indigent adults living with HIV infection. J Pain 2011;12(9):1004–16.

4 Lawson E, Sabin C, Perry N, et al. Is HIV painful? An epidemiologic study of the prevalence and risk factors for pain in HIV-infected patients. Clin J Pain 2014;31(9):813–9.

5 Nielsen CS, Staud R, Price DD. Individual differences in pain sensitivity: Measurement, causation, and consequences. J Pain 2009;10(3):231–7.

6 Holguin A, O'Connor KA, Biedenkapp J, et al. HIV-1 gp120 stimulates proinflammatory cytokine-mediated pain facilitation via activation of nitric oxide synthase-I (nNOS). Pain 2004;110(3):517–30.

7 Yuan SB, Shi Y, Chen J, et al. Gp120 in the pathogenesis of human immunodeficiency virus-associated pain. Ann Neurol 2014;75(6):837–50.

8 Milligan ED, Mehmert KK, Hinde JL, et al. Thermal hyperalgesia and mechanical allodynia produced by intrathecal administration of the human immunodeficiency virus-1 (HIV-1) envelope glycoprotein, gp120. Brain Res 2000;861(1):105–16.

9 US Department of Health and Human Services. 2016 HHS poverty guidelines. Washington, DC: Federal Register; 2016. Available at: https://aspe.hhs.gov/poverty-guidelines (accessed January 12, 2017).

10 Dickens C, McGowan L, Dale S. Impact of depression on experimental pain perception: A systematic review of the literature with meta-analysis. Psychosom Med 2003;65(3):369–75.

11 Quartana PJ, Campbell CM, Edwards RR. Pain catastrophizing: A critical review. Expert Rev Neurother 2009;9(5):745–58.

12 Ryscavage P, Kelly S, Li JZ, Harrigan PR, Taiwo B. Significance and clinical management of persistent low-level viremia and very-low-level viremia in HIV-1-infected patients. Antimicrob Agents Chemother 2014;58(7):3585–98.

13 Sarmati L, D'Ettorre G, Parisi SG, Andreoni M. HIV replication at low copy number and its correlation with the HIV reservoir: A clinical perspective. Current HIV Res 2015;13(3):250–7.

14 Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. Appl Psychol Meas 1977;1(3):385–401.

15 Sullivan MJL, Bishop SR, Pivik J. The pain catastrophizing scale: Development and validation. Psychol Assess 1995;7(4):524.

16 Fischer AA. Pressure algometry over normal muscles. Standard values, validity and reproducibility of pressure threshold. Pain 1987;30(1):115–26.

17 King CD, Sibille KT, Goodin BR, et al. Experimental pain sensitivity differs as a function of clinical pain severity in symptomatic knee osteoarthritis. Osteoarthritis Cartilage 2013;21(9):1243–52.

18 Aickin M, Gensler H. Adjusting for multiple testing when reporting research results: The Bonferroni vs Holm methods. Am J Public Health 1996;86(5): 726–8.

19 Latremoliere A, Woolf CJ. Central sensitization: A generator of pain hypersensitivity by central neural plasticity. J Pain 2009;10(9):895–926.

20 Woolf CJ. Central sensitization: Implications for the diagnosis and treatment of pain. Pain 2011;152(3 suppl):S2–15.

21 Gunthard HF, Saag MS, Benson CA, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2016 recommendations of the International Antiviral Society-USA Panel. JAMA 2016;316(2):191–210.

22 Mugavero MJ, Amico KR, Horn T, Thompson MA. The state of engagement in HIV care in the United States: From cascade to continuum to control. Clin Infect Dis 2013;57(8):1164–71.

23 Crepaz N, Tang T, Marks G, et al. Durable viral suppression and transmission risk potential among persons with diagnosed HIV infection: United States, 2012–2013. Clin Infect Dis 2016;63(7):976–83.

24 Merlin JS, Westfall AO, Raper JL, et al. Pain, mood, and substance abuse in HIV: Implications for clinic visit utilization, antiretroviral therapy adherence, and virologic failure. J Acquir Immune Defic Syndr 2012; 61(2):164–70.

25 Mugavero MJ, Napravnik S, Cole SR, et al. Viremia copy-years predicts mortality among treatment-naïve HIV-infected patients initiating antiretroviral therapy. Clin Infect Dis 2011;53(9):927–35.

26 Arenas-Pinto A, Bhaskaran K, Dunn D, Weller IV. The risk of developing peripheral neuropathy induced by nucleoside reverse transcriptase inhibitors decreases over time: Evidence from the Delta trial. Antiviral Ther 2008;13(2):289–95.

27 Lichtenstein KA, Armon C, Baron A, et al. Modification of the incidence of drug-associated symmetrical peripheral neuropathy by host and disease factors in the HIV outpatient study cohort. Clin Infect Dis 2005;40(1):148–57.