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Association between Pain, Pulmonary Function, and Respiratory Symptoms in People with HIV

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Abstract

Background: People with HIV (PWH) experience chronic pain and respiratory symptoms, which are closely related in the general population. Pain may impact the impaired pulmonary function seen in PWH beyond its association with HIV alone. Our objective was to investigate the relationship of pain severity to pulmonary function, respiratory symptoms, and sleep disturbance in PWH.

Setting: Study sites included the University of Pittsburgh, University of California San Francisco, and University of Washington.

Methods: Pain, dyspnea, and sleep were assessed using the Brief Chronic Pain Questionnaire, St. George's Respiratory Questionnaire (SGRQ), and Pittsburgh Sleep Quality Index. Participants performed pre- and post-bronchodilator spirometry and six-minute walk test. Associations between pain severity, lung function, dyspnea, and sleep were assessed with bivariate and multiple quartile regression analysis adjusted for age, sex, race, BMI, and smoking status.

Results: Of 159 PWH, median age was 56yr with 30.8% female. Two-thirds experienced pain in the past week, with 40.3% reporting chronic pain. Pain severity was higher with female sex (p=0.038), non-white race (p=0.005), current smoking (p=0.003), and lower $CD4^+$ count (p=0.035). In adjusted analysis, higher pain severity was correlated with reduced post-bronchodilator FEV1 %predicted (p=0.008), reduced post-bronchodilator FVC %predicted

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(p=0.019), and COPD (p=0.032). Greater pain severity was strongly associated with higher SGRQ score (p<0.001) and sleep disturbance (p<0.001).

Conclusion: In PWH, pain is common and associated with airflow obstruction, dyspnea, and sleep disturbance. Future studies assessing pain severity and pulmonary function over time could clarify the direction of this association and the impact on quality of life.

Keywords

HIV; pain; pulmonary function; dyspnea

Introduction

In the combination antiretroviral therapy (ART) era, people with HIV (PWH) have a near-normal life expectancy[1], yet experience a higher than expected number of comorbidities. Chronic pain is one such comorbidity[2-6] and is associated with impaired mobility and physical function in PWH[7,8]. Pulmonary function abnormalities and dyspnea are also common in PWH, with respiratory symptoms related to airflow obstruction[9], emphysema[10,11], and impaired diffusing capacity[12,13]. Abnormalities in pulmonary function have been associated with increased mortality[14,15] and decreased six-minute walk distance[16,17] in PWH. HIV is also recognized as an independent risk factor for chronic obstructive pulmonary disease (COPD)[18-22], although the prevalence of COPD in HIV cohorts has varied depending on use of tobacco, illicit drugs, and ART[10,23-27]. Finally, individuals with both HIV and COPD experience sleep disturbance[28-31], which can significantly impair quality of life and worsen pain.

Chronic pain, sleep disturbance, and respiratory comorbidities have been linked, yet their relationship is not well-understood in HIV[32-35]. It is clear that pain and lung disease are closely related, and pain may impact the impaired pulmonary function and dyspnea seen in PWH beyond what HIV itself is known to do. Understanding the relationship between these comorbidities could help identify more effective interventions to improve quality of life in PWH. We investigated associations between pain, respiratory symptoms, and pulmonary function in a US cohort of PWH. Our objective was to relate the presence and severity of pain to measures of lung function, respiratory symptoms, and sleep disturbance.

Methods

Participants from the Pittsburgh HIV Lung Cohort[23,36] enrolled from outpatient clinics at the University of Pittsburgh, University of California San Francisco, and University of Washington were included. Subjects with HIV infection, age ≥ 18 years, were recruited between 2015-2019. The study protocol was approved by the Institutional Review Boards of all participating institutions, and all participants signed written, informed consent. At the study visit, demographics, smoking history, illicit drug use, current ART, and comorbidities were collected by standardized participant interview. Participants underwent pulmonary function testing (PFT) and completed a pain questionnaire on the same day. Peripheral $CD4^+$ counts and plasma HIV RNA levels (viral load) were confirmed by chart review or direct testing within 6 months from the study visit.

A two-item brief chronic pain questionnaire was completed asking about pain duration and severity (none, very mild, mild, moderate, severe, very severe)[37,38]. Pain was considered chronic if present for >3 months. Individuals who indicated the presence of at least mild pain for >3 months also described its location and completed the three-question Pain, Enjoyment, General Activity (PEG) Scale, with each question scored between 0-10. Participants completed the Pittsburgh Sleep Quality Index (PSQI), evaluating sleep in seven different domains over a one-month period[39], with each domain scored from 0-3. Higher numbers indicated worse sleep.

Study participants performed spirometry before and after bronchodilator administration, including forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC)[40], and diffusing capacity for carbon monoxide (DLCO)[41] following the American Thoracic Society/European Respiratory Society standards[42]. DLCO was corrected for hemoglobin and carboxyhemoglobin[42]. Hankinson and Neas equations were used to determine percent predicted values of spirometry and DLCO measurements, respectively[42,43]. COPD was defined as a post-bronchodilator FEV1/FVC ratio less than 0.70 based on the Global Initiative for Chronic Obstructive Lung Disease[44].

The majority of participants (93.7%) also performed a six-minute walk test (6MWT) with distance measured in meters[45] to assess impact of pain on exercise capacity. All participants completed the St. George's Respiratory Questionnaire (SGRQ), a validated 50-item questionnaire that measures the impact of respiratory symptoms on overall health, daily life, and perception of well-being (scored from 0-100 with higher scores indicating more limitations)[46,47].

Statistical Analysis

Descriptive statistics were performed to visualize demographic data. Pain severity responses were translated into scores of 0-5, with higher scores indicating more severe pain. The sum of the seven scores in the PSQI was reported, with a score ≥ 5 indicating a "poor" sleeper. Associations between pain severity and lung function (FEV1 %predicted, FVC %predicted, DLCO %predicted), 6MWT, PSQI, and SGRQ were assessed with bivariate and multiple quartile regression analysis. Results of associations were reported with a coefficient, the difference in medians between groups, with a coefficient of zero indicating no difference. Regression analyses were adjusted for age, sex, race, BMI, and smoking status. The confounders were selected based on the established association of these variables with the measured outcomes[39,48-50]. Statistical analysis was carried out using Stata 16.0 (StataCorp LLC, College Station, Texas).

Results

One hundred fifty-nine PWH were enrolled. Most participants (69.2%) were male, aged ≥ 55 (59.7%), and 47.2% were black (Table 1). Over 60% were overweight or obese/morbidly obese (median BMI 26.6). More than two-thirds (69.2%) had ever smoked, with 47.2% currently smoking. The majority (86.8%) reported current or prior illicit drug use. Self-reported comorbid medical conditions included diabetes mellitus (18.2%), cancer (18.2%), hepatitis C virus (24.5%), and sleep apnea (15.7%). Nearly all (92.5%) were taking ART. In

the 143 participants with HIV viral loads, 19.6% had detectable viremia (>40 copies/mL). In the 111 participants with $CD4^+$ counts, median $CD4^+$ count was 646 cells/mm^3, and 86.5% had a $CD4^+$ count ≥350 cells/mm^3.

Mean values for post-bronchodilator FEV1 %predicted, FVC %predicted, and FEV1/FVC ratio overall were normal (Table 1). Thirty-eight (24.4%) participants met the definition of COPD, though only half of these individuals reported a known clinical diagnosis of COPD. Overall, mean DLCO value was mildly reduced (78.4% predicted), with 51.6% of participants demonstrating an abnormal DLCO (DLCO %predicted<80).

One hundred forty-nine participants completed the 6MWT with a median distance of 448m (range 183-683m). Expected walk distances for this cohort based on reference equations for 6MWT in healthy adults ranged from 335-837m with a median of 570m[51]. Participants walked on average 139m less than expected (p<0.001). All participants completed the SGRQ with a median score of 8.7 (IQR 2.9 – 19.9), consistent with mild symptoms[52]. The median PSQI score was 7 (IQR 4 – 9), indicating poor sleep in the majority of participants.

Two-thirds of participants reported having any pain in the past one week, with 46% reporting at least mild pain (Table 1). The prevalence of pain increased with age. More than one-third (40.3%) of participants reported chronic pain. Of the 52 participants with chronic pain who completed additional questions, 50% reported low back pain and 30.8% reported paresthesias in the hands/feet. PEG scores showed moderate interference of pain in general activity (median score 4.5) and enjoyment of life (median score 4).

Pain severity was higher with female sex (p=0.038), non-white race (p=0.005), and current smoker status (p=0.003) (Table 2). Higher pain score was correlated with lower $CD4^+$ count (p=0.035). No associations were found between pain severity and age, BMI, former smoker status, or detectable viremia. There was no association between pain severity and the presence of self-reported comorbidities: pulmonary hypertension (p=0.719), diabetes (p>0.9), cancer (p>0.9), or history of tuberculosis (p=0.289). After adjustment for age, sex, race, BMI, and smoking status, higher pain severity was correlated with lower post-bronchodilator FEV1 %predicted (coefficient=−2.21, p=0.008, Table 2). Higher pain score was also associated with lower post-bronchodilator FVC %predicted (p=0.019) and the presence of COPD (p=0.032) after adjustment for these covariates. While the relationship between pain severity and DLCO %predicted did not achieve statistical significance (p=0.062), there was a trend toward significance and the coefficient size was comparable to that for FEV1 %predicted and FVC %predicted. Pain severity was not significantly correlated with adjusted 6MWT distance (p>0.9). Higher SGRQ score was strongly correlated to greater pain severity in both unadjusted and adjusted models (p<0.001). Higher PSQI score was significantly associated with greater pain severity in both unadjusted and adjusted (both p<0.001) models (Table 2). Higher SGRQ score was also associated with reduced post-bronchodilator FEV1 %predicted (p=0.009) and reduced FEV1/FVC ratio (p=0.002) when adjusted for covariates. The presence of pain did not modify these relationships.

Discussion

We found that greater pain severity was associated with worse pulmonary function and sleep quality in PWH. Pain severity was significantly associated with reduced post-bronchodilator FEV1 %predicted, reduced post-bronchodilator FVC %predicted, and the presence of COPD. We also detected a trend toward an association between pain severity and reduced DLCO %predicted. Additionally, pain was strongly correlated with a higher prevalence of respiratory symptoms and with poor sleep. Despite the established relationship between pain and functional limitations in HIV[7], we did not identify a significant correlation between pain severity and 6MWT distance.

Our finding of pain in two-thirds of participants is consistent with literature demonstrating high levels of pain in PWH[2-4,6]. Female sex, non-white race, current smoking status, and lower $CD4^+$ count were significant predictors of pain in our cohort, though these associations are inconsistent in other populations due to variability in participant demographics and limitations of retrospective cross-sectional analyses.

The novel relationships we identified among measures of pain, pulmonary function, and respiratory symptoms are highly relevant given the frequent co-existence of these comorbidities. Associations between lung function and pain have been investigated in COPD, yet findings are inconsistent[53-58]. There is, however, a strong correlation between pain and breathlessness in COPD, in both quantitative and qualitative analyses[53,56,58,59].

Impaired lung function, symptoms, and pain may be linked in HIV via common underlying causes. Pain and dyspnea are intimately associated[32], and the presence of pain within the neck, thorax, and abdomen may alter respiratory mechanics due to impaired chest wall excursion, leading to breathlessness, obstruction, and restriction[59]. Alternately, parenchymal destruction, decreased elasticity, airway inflammation, and airway narrowing – known to occur in PWH[10-13] – may lead to airflow obstruction and cough, precipitating increased respiratory muscle work of breathing and pain[60]. Pain, pulmonary function impairment, and dyspnea have each also been associated with increased systemic inflammation[61-63], and the increase in pro-inflammatory cytokines known to occur in HIV[64] may contribute to an increase in each of these comorbidities. Finally, the presence of depression is strongly correlated with both pain and dyspnea[65,66]. The high frequency of depression in PWH[67,68] may also provide a link between the concurrent pain and dyspnea these individuals experience.

In our cohort, most individuals also experienced sleep disturbance. Pain severity was highly correlated to worse PSQI score, yet we found no significant indirect effect of pulmonary function on sleep (data not shown), suggesting that the relationship between pain and sleep impairment is independent of pulmonary function. In our cohort and other studies[69,70], insomnia in PWH appears to be more severe in those with pain, but pulmonary function as a potential mediator has not been previously investigated.

A better understanding of the relationships between pain, lung function, and sleep has substantial clinical relevance in the care of PWH. Identifying these common comorbidities during primary care visits provides an opportunity to improve quality of life, as treatment of

pain may impact an individual's perception of dyspnea and vice versa. These concepts will need to be assessed in prospective studies evaluating pain severity and pulmonary function on a longitudinal basis after implementation of specific therapies addressing pain management and/or dyspnea.

There are several limitations to our research. Most importantly, causation between pain and pulmonary factors cannot be established due to our study's cross-sectional nature. Additionally, our selection of participants from outpatient clinic may bias our analysis toward healthier individuals. As such, those sampled may not be representative of the overall HIV-infected population in the United States. Our data collection did not include information on pharmacologic pain management, thus pain could be underreported by individuals successfully treated with chronic pain medications. Finally, we did not have objective measures of psychological factors such as depression and anxiety that could confound the associations between pain and respiratory symptoms.

Conclusions

Our study investigating pain in a cohort of HIV-infected adults in the US demonstrates that increased levels of pain in PWH correlate to airflow obstruction, worsening respiratory symptoms, and sleep disturbance. Future studies should assess serial measures of pain severity and pulmonary function over time to clarify the direction of this association and underlying mechanisms.

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References

1. Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet. 2008;372(9635):293–299. doi:10.1016/S0140-6736(08)61113-7 [PubMed: 18657708]
2. 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. 2015;31(9):813–819. doi:10.1097/AJP.0000000000000162 [PubMed: 25329144]
3. 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(9):1004–1016. doi:10.1016/j.jpain.2011.04.002 [PubMed: 21684218]
4. 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. doi:10.1111/j.1526-4637.2010.00802.x [PubMed: 20210870]
5. 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):164–170. doi:10.1097/QAI.0b013e3182662215 [PubMed: 22766967]
6. Parker R, Stein DJ, Jelsma J. Pain in people living with HIV/AIDS: a systematic review. J Int AIDS Soc. 2014;17:18719. doi:10.7448/IAS.17.1.18719 [PubMed: 24560338]

7. 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):1985–1993. doi:10.1111/pme.12255 [PubMed: 24119077]
8. Ellis RJ, Rosario D, Clifford DB, et al. Continued high prevalence and adverse clinical impact of human immunodeficiency virus-associated sensory neuropathy in the era of combination antiretroviral therapy: the CHARTER Study. Arch Neurol. 2010;67(5):552–558. doi:10.1001/archneurol.2010.76 [PubMed: 20457954]
9. Pefura-Yone EW, Fodjeu G, Kengne AP, Roche N, Kuaban C. Prevalence and determinants of chronic obstructive pulmonary disease in HIV infected patients in an African country with low level of tobacco smoking. Respir Med. 2015;109(2):247–254. doi:10.1016/j.rmed.2014.12.003 [PubMed: 25538018]
10. Sampériz G, Guerrero D, López M, et al. Prevalence of and risk factors for pulmonary abnormalities in HIV-infected patients treated with antiretroviral therapy. HIV Med. 2014;15(6):321–329. doi:10.1111/hiv.12117 [PubMed: 24314004]
11. Guaraldi G, Besutti G, Scaglioni R, et al. The burden of image based emphysema and bronchiolitis in HIV-infected individuals on antiretroviral therapy. PLoS One. 2014;9(10):e109027. doi:10.1371/journal.pone.0109027 [PubMed: 25354261]
12. Crothers K, McGinnis K, Kleerup E, et al. HIV infection is associated with reduced pulmonary diffusing capacity. J Acquir Immune Defic Syndr. 2013;64(3):271–278. doi:10.1097/QAI.0b013e3182a9215a [PubMed: 23979001]
13. Fitzpatrick ME, Gingo MR, Kessinger C, et al. HIV infection is associated with diffusing capacity impairment in women. J Acquir Immune Defic Syndr. 2013;64(3):284–288. doi:10.1097/QAI.0b013e3182a9213a [PubMed: 23979000]
14. Triplette M, Justice A, Attia EF, et al. Markers of chronic obstructive pulmonary disease are associated with mortality in people living with HIV. AIDS. 2018;32(4):487–493. doi:10.1097/QAD.0000000000001701 [PubMed: 29135579]
15. Gingo MR, Nouraie M, Kessinger CJ, et al. Decreased lung function and all-cause mortality in HIV-infected individuals. Annals of the American Thoracic Society. 2018;15(2):192–199. doi:10.1513/AnnalsATS.201606-492OC [PubMed: 29313714]
16. Campo M, Oursler KK, Huang L, et al. Association of chronic cough and pulmonary function with 6-minute walk test performance in HIV infection. J Acquir Immune Defic Syndr. 2014;65(5):557–563. doi:10.1097/QAI.0000000000000086 [PubMed: 24346638]
17. Robertson TE, Nouraie M, Qin S, et al. HIV infection is an independent risk factor for decreased 6-minute walk test distance. PLoS One. 2019;14(4):e0212975. doi:10.1371/journal.pone.0212975 [PubMed: 31017909]
18. Bigna JJ, Kenne AM, Asangbeh SL, Sibetcheu AT. Prevalence of chronic obstructive pulmonary disease in the global population with HIV: a systematic review and meta-analysis. Lancet Glob Health. 2018;6(2):e193–e202. doi:10.1016/S2214-109X(17)30451-5 [PubMed: 29254748]
19. Crothers K, Huang L, Goulet JL, et al. HIV infection and risk for incident pulmonary diseases in the combination antiretroviral therapy era. Am J Respir Crit Care Med. 2011;183(3):388–395. doi:10.1164/rccm.201006-0836OC [PubMed: 20851926]
20. Crothers K, Butt AA, Gibert CL, et al. Increased COPD among HIV-positive compared to HIV-negative veterans. Chest. 2006;130(5):1326–1333. doi:10.1378/chest.130.5.1326 [PubMed: 17099007]
21. Drummond MB, Merlo CA, Astemborski J, et al. The effect of HIV infection on longitudinal lung function decline among IDUs: a prospective cohort. AIDS. 2013;27(8):1303–1311. doi:10.1097/QAD.0b013e32835e395d [PubMed: 23299176]
22. Drummond MB, Kunisaki KM, Huang L. Obstructive lung diseases in HIV: A clinical review and identification of key future research needs. Semin Respir Crit Care Med. 2016;37(2):277–288. doi:10.1055/s-0036-1578801 [PubMed: 26974304]
23. Gingo MR, George MP, Kessinger CJ, et al. Pulmonary function abnormalities in HIV-infected patients during the current antiretroviral therapy era. Am J Respir Crit Care Med. 2010;182(6):790–796. doi:10.1164/rccm.200912-1858OC [PubMed: 20522793]

24. George MP, Kannass M, Huang L, Sciurba FC, Morris A. Respiratory symptoms and airway obstruction in HIV-infected subjects in the HAART era. PLoS One. 2009;4(7):e6328. doi:10.1371/journal.pone.0006328 [PubMed: 19621086]
25. Ronit A, Lundgren J, Afzal S, et al. Airflow limitation in people living with HIV and matched uninfected controls. Thorax. 2018;73(5):431–438. doi:10.1136/thoraxjnl-2017-211079 [PubMed: 29331988]
26. Kunisaki KM, Nouraie M, Jensen RL, et al. Lung function in men with and without HIV. AIDS. 2020;34(8):1227–1235. doi:10.1097/QAD.0000000000002526 [PubMed: 32287070]
27. Makinson A, Hayot M, Eymard-Duvernay S, et al. HIV is associated with airway obstruction: a matched controlled study. AIDS. 2018;32(2):227–232. doi:10.1097/QAD.0000000000001691 [PubMed: 29135582]
28. Gutierrez J, Tedaldi EM, Armon C, Patel V, Hart R, Buchacz K. Sleep disturbances in HIV-infected patients associated with depression and high risk of obstructive sleep apnea. SAGE Open Med. 2019;7:2050312119842268. doi:10.1177/2050312119842268 [PubMed: 31001423]
29. Norman SE, Resnick L, Cohn MA, Duara R, Herbst J, Berger JR. Sleep disturbances in HIV-seropositive patients. JAMA. 1988;260(7):922.
30. McSharry DG, Ryan S, Calverley P, Edwards JC, McNicholas WT. Sleep quality in chronic obstructive pulmonary disease. Respirology. 2012;17(7):1119–1124. doi:10.1111/j.1440-1843.2012.02217.x [PubMed: 22758620]
31. Rennard S, Decramer M, Calverley PMA, et al. Impact of COPD in North America and Europe in 2000: subjects' perspective of Confronting COPD International Survey. Eur Respir J. 2002;20(4):799–805. doi:10.1183/09031936.02.03242002 [PubMed: 12412667]
32. Clark N, Fan VS, Slatore CG, et al. Dyspnea and pain frequently co-occur among Medicare managed care recipients. Annals of the American Thoracic Society. 2014;11(6):890–897. doi:10.1513/AnnalsATS.201310-369OC [PubMed: 24960243]
33. Bentsen SB, Rustøen T, Miaskowski C. Prevalence and characteristics of pain in patients with chronic obstructive pulmonary disease compared to the Norwegian general population. J Pain. 2011;12(5):539–545. doi:10.1016/j.jpain.2010.10.014 [PubMed: 21549316]
34. Mathias JL, Cant ML, Burke ALJ. Sleep disturbances and sleep disorders in adults living with chronic pain: a meta-analysis. Sleep Med. 2018;52:198–210. doi:10.1016/j.sleep.2018.05.023 [PubMed: 30314881]
35. Janssen DJA, Spruit MA, Uszko-Lencer NH, Schols JMGA, Wouters EFM. Symptoms, comorbidities, and health care in advanced chronic obstructive pulmonary disease or chronic heart failure. J Palliat Med. 2011;14(6):735–743. doi:10.1089/jpm.2010.0479 [PubMed: 21510771]
36. Qin S, Vodovotz L, Zamora R, et al. Association Between Inflammatory Pathways and Phenotypes of Pulmonary Dysfunction Using Cluster Analysis in Persons Living With HIV and HIV-Uninfected Individuals. J Acquir Immune Defic Syndr. 2020;83(2):189–196. doi:10.1097/QAI.0000000000002234 [PubMed: 31929407]
37. Merlin JS, Westfall AO, Chamot E, et al. Quantitative Evaluation of an Instrument to Identify Chronic Pain in HIV-Infected Individuals. AIDS Res Hum Retroviruses. 2015;31(6):623–627. doi:10.1089/AID.2014.0362 [PubMed: 25693683]
38. Merlin JS, Walcott MM, Herbey I, et al. Qualitative investigation of a Brief Chronic Pain Screening tool in HIV-infected patients. AIDS Patient Care STDS. 2014;28(4):176–182. doi:10.1089/apc.2014.0006 [PubMed: 24621145]
39. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193–213. doi:10.1016/0165-1781(89)90047-4 [PubMed: 2748771]
40. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319–338. doi:10.1183/09031936.05.00034805 [PubMed: 16055882]
41. Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J. 2005;26(4):720–735. doi:10.1183/09031936.05.00034905 [PubMed: 16204605]

42. Neas LM, Schwartz J. The determinants of pulmonary diffusing capacity in a national sample of U.S. adults. Am J Respir Crit Care Med. 1996;153(2):656–664. doi:10.1164/ajrccm.153.2.8564114 [PubMed: 8564114]
43. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med. 1999;159(1):179–187. doi:10.1164/ajrccm.159.1.9712108 [PubMed: 9872837]
44. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2019 report. http://www.goldcopd.org. Accessed May 4, 2020.
45. Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpreting small differences in functional status: the Six Minute Walk test in chronic lung disease patients. Am J Respir Crit Care Med. 1997;155(4):1278–1282. doi:10.1164/ajrccm.155.4.9105067 [PubMed: 9105067]
46. Jones PW, Quirk FH, Baveystock CM. The st george's respiratory questionnaire. Respir Med. 1991;85 Suppl B:25–31; discussion 33. doi:10.1016/s0954-6111(06)80166-6 [PubMed: 1759018]
47. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. Am Rev Respir Dis. 1992;145(6):1321–1327. doi:10.1164/ajrccm/145.6.1321 [PubMed: 1595997]
48. Ferrer M, Villasante C, Alonso J, et al. Interpretation of quality of life scores from the St George's Respiratory Questionnaire. Eur Respir J. 2002;19(3):405–413. doi:10.1183/09031936.02.00213202 [PubMed: 11936515]
49. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111–117. doi:10.1164/ajrccm.166.1.at1102 [PubMed: 12091180]
50. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26(5):948–968. doi:10.1183/09031936.05.00035205 [PubMed: 16264058]
51. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. Am J Respir Crit Care Med. 1998;158(5 Pt 1):1384–1387. doi:10.1164/ajrccm.158.5.9710086 [PubMed: 9817683]
52. Jones PW, Brusselle G, Dal Negro RW, et al. Properties of the COPD assessment test in a cross-sectional European study. Eur Respir J. 2011;38(1):29–35. doi:10.1183/09031936.00177210 [PubMed: 21565915]
53. Borge CR, Wahl AK, Moum T. Association of breathlessness with multiple symptoms in chronic obstructive pulmonary disease. J Adv Nurs. 2010;66(12):2688–2700. doi:10.1111/j.1365-2648.2010.05447.x [PubMed: 20825511]
54. Borge CR, Wahl AK, Moum T. Pain and quality of life with chronic obstructive pulmonary disease. Heart Lung. 2011;40(3):e90–101. doi:10.1016/j.hrtlng.2010.10.009 [PubMed: 21444112]
55. Roberts MH, Mapel DW, Hartry A, Von Worley A, Thomson H. Chronic pain and pain medication use in chronic obstructive pulmonary disease. A cross-sectional study. Annals of the American Thoracic Society. 2013;10(4):290–298. doi:10.1513/AnnalsATS.201303-040OC [PubMed: 23952846]
56. van Dam van Isselt EF, Groenewegen-Sipkema KH, Spruit-van Eijk M, et al. Pain in patients with COPD: a systematic review and meta-analysis. BMJ Open. 2014;4(9):e005898. doi:10.1136/bmjopen-2014-005898
57. Janssen DJA, Wouters EFM, Parra YL, Stakenborg K, Franssen FME. Prevalence of thoracic pain in patients with chronic obstructive pulmonary disease and relationship with patient characteristics: a cross-sectional observational study. BMC Pulm Med. 2016;16:47. doi:10.1186/s12890-016-0210-8 [PubMed: 27052199]
58. Bentsen SB, Rustøen T, Miaskowski C. Differences in subjective and objective respiratory parameters in patients with chronic obstructive pulmonary disease with and without pain. Int J Chron Obstruct Pulmon Dis. 2012;7:137–143. doi:10.2147/COPD.S28994 [PubMed: 22419861]
59. Lohne V, Heer HCD, Andersen M, Miaskowski C, Kongerud J, Rustøen T. Qualitative study of pain of patients with chronic obstructive pulmonary disease. Heart Lung. 2010;39(3):226–234. doi:10.1016/j.hrtlng.2009.08.002 [PubMed: 20457343]

60. MacIntyre NR. Muscle dysfunction associated with chronic obstructive pulmonary disease. Respir Care. 2006;51(8):840–7; discussion 848. [PubMed: 16867196]
61. Gan WQ, Man SFP, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax. 2004;59(7):574–580. doi:10.1136/thx.2003.019588 [PubMed: 15223864]
62. Su B, Liu T, Fan H, et al. Inflammatory Markers and the Risk of Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. PLoS One. 2016;11(4):e0150586. doi:10.1371/journal.pone.0150586 [PubMed: 27104349]
63. Merlin JS, Westfall AO, Heath SL, et al. Brief Report: IL-1β Levels Are Associated With Chronic Multisite Pain in People Living With HIV. J Acquir Immune Defic Syndr. 2017;75(4):e99–e103. doi:10.1097/QAI.0000000000001377 [PubMed: 28328552]
64. Kedzierska K, Crowe SM. Cytokines and HIV-1: interactions and clinical implications. Antivir Chem Chemother. 2001;12(3):133–150. doi:10.1177/095632020101200301 [PubMed: 12959322]
65. Ryerson CJ, Arean PA, Berkeley J, et al. Depression is a common and chronic comorbidity in patients with interstitial lung disease. Respirology. 2012;17(3):525–532. doi:10.1111/j.1440-1843.2011.02122.x [PubMed: 22221976]
66. Bentsen SB, Gundersen D, Assmus J, Bringsvor H, Berland A. Multiple symptoms in patients with chronic obstructive pulmonary disease in Norway. Nurs Health Sci. 2013;15(3):292–299. doi:10.1111/nhs.12031 [PubMed: 23350753]
67. Cruess DG, Evans DL, Repetto MJ, Gettes D, Douglas SD, Petitto JM. Prevalence, diagnosis, and pharmacological treatment of mood disorders in HIV disease. Biol Psychiatry. 2003;54(3):307–316. doi:10.1016/s0006-3223(03)00318-4 [PubMed: 12893106]
68. Scott W, Arkuter C, Kioskli K, et al. Psychosocial factors associated with persistent pain in people with HIV: a systematic review with meta-analysis. Pain. 2018;159(12):2461–2476. doi:10.1097/j.pain.0000000000001369 [PubMed: 30130299]
69. Aouizerat BE, Miaskowski CA, Gay C, et al. Risk factors and symptoms associated with pain in HIV-infected adults. J Assoc Nurses AIDS Care. 2010;21(2):125–133. doi:10.1016/j.jana.2009.10.003 [PubMed: 20116299]
70. Phillips TJC, Brown M, Ramirez JD, et al. Sensory, psychological, and metabolic dysfunction in HIV-associated peripheral neuropathy: A cross-sectional deep profiling study. Pain. 2014;155(9):1846–1860. doi:10.1016/j.pain.2014.06.014 [PubMed: 24973717]

Table 1.

Participant demographics, baseline characteristics, and pain prevalence

Number of participants, n	159
Age (y), median (p25, p75, range)	56 (50, 60, 25-81)
Age groups, n (%)	
25-34	9 (5.7)
35-44	10 (6.3)
45-54	45 (28.3)
≥55	95 (59.7)
Male, n (%)	110 (69.2)
Female, n (%)	49 (30.8)
Race, n (%)	
White	70 (44.0)
Black	75 (47.2)
Other	14 (8.8)
BMI (kg/m^2), mean (SD)	27.6 (6.5)
Underweight (< 18.5)	3 (1.9)
Normal (≥18.5, < 25)	59 (37.1)
Overweight (≥25, < 30)	52 (32.7)
Obese/Morbidly Obese (≥ 30)	45 (28.3)
Smoking status, n (%)	
Current smoker	75 (47.2)
Prior smoker	35 (22.0)
Never smoker	49 (30.8)
History illicit drug use, n (%)	138 (86.8)
Detectable viral load (>40 copies/mL), n (%), n=143	28 (19.6)
Latest CD4$^+$ count (cells/mm^3), median (p25, p75, range), n=111	646 (442, 847, 0-1546)
CD4$^+$ ranges, n (%)	
< 200	8 (7.2)
200-349	7 (6.3)
≥ 350	96 (86.5)
Currently receiving ART, n (%)	147 (92.5)
Comorbidities (self-reported), n (%)	
Diabetes	29 (18.2)
Cancer	29 (18.2)
COPD	28 (17.6)
Hepatitis C	39 (24.5)
Sleep apnea	25 (15.7)
Pulmonary hypertension	1 (0.6)
Pulmonary tuberculosis	10 (6.3)
Pulmonary function testing	
FEV1 %predicted, mean (SD), n=155	90.7 (21.5)

FVC %predicted, mean (SD), n=155	93.1 (18.3)
FEV1/FVC ratio, mean (SD), n=156	0.76 (0.1)
FEV1/FVC ratio < 0.7, n (%)	38 (24.4)
DLCO %predicted, mean (SD), n=153	78.4 (18.4)
DLCO <0.8, n (%), n=153	79 (51.6)
6MWT distance (m), median (p25, p75, range), n=149	448 (373, 492, 183-683)
Expected walk distance (m), median (p25, p75, range), n=159	570 (515, 633, 335-837)
SGRQ score, median (p25, p75, range), n=159	8.7 (2.9, 19.9, 0-67.4)
PSQI, median (p25, p75, range), n=158	7 (4, 9, 1-16)
Pain in last one week, n (%)	
None	53 (33.3)
Very mild	33 (20.8)
Mild	30 (18.9)
Moderate	29 (18.2)
Severe	12 (7.5)
Very severe	2 (1.3)
Pain prevalence by age, n (%), n=106	
25-34	4 (3.8)
35-44	7 (6.6)
45-54	32 (30.2)
≥55	63 (59.4)
Pain lasting > 3 months (chronic pain), n (%)	64 (40.3)

BMI = body mass index, SD = standard deviation, ART = antiretroviral therapy, FEV1 = forced vital capacity in one second, FVC = forced vital capacity, DLCO = diffusion limitation of carbon monoxide, 6MWT = six-minute walk test, SGRQ = St. George's Respiratory Questionnaire, PSQI = Pittsburgh Sleep Quality Index

Table 2.

Association between pain severity and demographic/pulmonary factors from quartile regression analysis

	Unadjusted		Adjusted for age, sex, race, BMI, and smoking status			
	Coefficient	**P value**	**Coefficient**	**95% CI**		**P value**
Age	0	>0.900				
Female	1.000	0.038				
BMI	0	>0.900				
White race	−1.000	0.005				
Current smoker	0.330	0.003				
Former smoker	0	>0.900				
$CD4^+$ count (n=111)	−0.001	0.035				
Detectable viral load (n=143)	1.000	0.080				
FEV1 %predicted (n=155)	−1.610	0.035	−2.210	−3.840	−0.570	0.008
FVC %predicted (n=155)	−2.450	0.005	−2.430	−4.450	−0.410	0.019
FEV1/FVC (n=156)	0	>0.900	0	−3.770	3.770	>0.900
COPD	1.000	0.018	1.000	0.090	1.910	0.032
DLCO %predicted (n=153)	0	>0.900	−2.130	−4.370	0.110	0.062
6MWT distance (n=149)	0	>0.900	0	−0.010	0.010	>0.900
SGRQ score (n=159)	0.040	0.002	0.050	0.030	0.080	<0.001
PSQI (n=158)	0.180	<0.001	0.150	0.070	0.230	<0.001

Coefficient = difference in median between groups; coefficient of 0 indicates no difference. Abbreviations: 95% CI = 95% confidence interval, BMI = body mass index, FEV1 = forced vital capacity in one second, FVC = forced vital capacity, COPD = chronic obstructive pulmonary disease, defined as FEV1/FVC < 0.7, DLCO = diffusion limitation of carbon monoxide, 6MWT = six-minute walk test, SGRQ = St. George's Respiratory Questionnaire, PSQI = Pittsburgh Sleep Quality Index