

# Symptoms of Autonomic Dysfunction in Human Immunodeficiency Virus

Dominic Chow,<sup>1</sup> Beau K. Nakamoto,<sup>1,2</sup> Katherine Sullivan,<sup>1</sup> David M. Sletten,<sup>3</sup> Satomi Fujii,<sup>1</sup> Sari Umekawa,<sup>1</sup> Morgan Kocher,<sup>1</sup> Kalpana J. Kallianpur,<sup>1</sup> Cecilia M. Shikuma,<sup>1</sup> and Phillip Low<sup>3</sup>

<sup>1</sup>Hawaii Center for AIDS, Department of Medicine, University of Hawaii, and <sup>2</sup>Straub Clinic and Hospital, Department of Neurology, Honolulu, Hawaii; and <sup>3</sup>Mayo Clinic, Rochester, Minnesota

**This retrospective study evaluated the frequencies of symptoms associated with autonomic dysfunction in human immunodeficiency virus (HIV)-infected patients on stable combined antiretroviral therapy. Patients infected with HIV reported higher frequencies of dysautonomia symptoms compared with HIV-negative patients, particularly in the autonomic domains related to urinary, sleep, gastroparesis, secretomotor, pupillomotor, and male sexual dysfunction.**

**Keywords.** autonomic dysfunction; dysautonomia; HIV.

Autonomic dysfunction (AD) is common in patients infected with human immunodeficiency virus (HIV) and can result in symptoms such as orthostatic intolerance, gastrointestinal abnormalities, and male sexual dysfunction, which substantially impacts quality of life [1]. Human immunodeficiency virus-infected individuals with symptomatic autonomic neuropathy have increased morbidity [2]. In the prehighly active antiretroviral therapy (ART) era, AD in patients infected with HIV was associated with longer duration of infection, uncontrolled HIV viremia, and exposure to older antiretroviral medications [3]. Combined ART (cART) has decreased the morbidity and mortality associated with immunosuppression [1]. However, the impact of cART on the prevalence of AD and its associated symptoms is unclear. This study aimed to determine the

prevalence of symptoms of AD in virologically suppressed HIV-infected patients on cART.

## METHODS

### Study Design and Population

This is a substudy of the Hawaii Aging with HIV Cardiovascular Study, a longitudinal study of the role of oxidative stress and inflammation in HIV-associated cardiovascular risk [4]. Human immunodeficiency virus-positive patients on stable cART >3 months without prior cardiovascular disease, arrhythmia, or diabetes were recruited. Patients with hepatitis C virus (HCV) infection confirmed by presence of HCV antibody, hospitalization within 14 days before study entry, and active drug and alcohol abuse were excluded. Height, weight, body mass index, blood pressure, waist-to-hip ratio, electrocardiogram, fasting lipids, and 2-hour glucose tolerance were measured. Self-reported current and past smoking status was obtained. A convenient sample of HIV-seronegative patients who were often partners or friends of enrolled HIV-infected patients were recruited as a comparison group. Signed consent for study participation was obtained, and institutional review board approval was obtained from the University of Hawaii.

### Formal Assessment of Autonomic Symptoms

Symptoms of AD were obtained with the Autonomic Symptom Profile (ASP), a 169-item validated questionnaire of symptoms across 11 domains of autonomic function [5]. The 11 domains with examples of symptoms are as follows: Orthostatic intolerance (light-headedness/dizziness on standing); Secretomotor (abnormal sweating, inability to tolerate heat and mucosal secretory dysfunction such as dry eyes/mouth); Urinary (urinary frequency/urgency, incontinence, or urinary retention); Gastroparesis (bloating, nausea, and vomiting); Diarrhea; Constipation; Pupillomotor (light sensitivity, visual blurring and pupillomotor dysfunction); Vasomotor (excessively cold hands/feet with discoloration resulting from peripheral sympathetic dysfunction); Reflex syncope (fainting); Sleep function (disturbance in sleep); and Male sexual dysfunction (difficulty with erection/ejaculation).

A score for each domain and a total Composite Autonomic Symptoms Scale (COMPASS) score were calculated from the ASP responses [5, 6]. A COMPASS score  $\geq 30$  suggests significant clinical AD [7].

### Assessment of Autonomic Function

Formal autonomic function was assessed using a battery of standardized tests that assessed 3 areas of autonomic function:

Received 17 April 2015; accepted 3 July 2015.

Correspondence: Dominic Chow, MD, Professor of Medicine, Hawaii Center for AIDS, John A. Burns School of Medicine, University of Hawaii at Manoa, 651 Ilalo St., Biomedical Sciences Building 231, Honolulu, HI 96813 (dominicc@hawaii.edu).

#### Open Forum Infectious Diseases

© The Author 2015. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact [journals.permissions@oup.com](mailto:journals.permissions@oup.com).

DOI: 10.1093/ofid/ofv103

cardiovascular, adrenergic, and sudomotor. Patients fasted more than 8 hours, avoided heavy exercise more than 1 day before testing, and did not ingest caffeine, nicotine, or medication that might affect the test results [6]. The autonomic test battery were transformed into the Composite Autonomic Scoring Scale (CASS), a functional scale different from the questionnaire-derived COMPASS [5]. The Composite Autonomic Scoring Scale quantitates autonomic function into a 10-point scale and can validate COMPASS findings. A score  $\leq 3$  indicates no or mild autonomic failure, 4–6 indicates moderate failure, and  $\geq 7$  indicates severe failure.

### Statistical Analysis

The objective of this study was to compare the prevalence and characteristics of autonomic symptoms between HIV-positive and HIV-negative patients. Categorical variables, including symptom frequencies, were compared using the  $\chi^2$  test. Continuous variables are presented as medians along with interquartile range (Q<sub>1</sub>, Q<sub>3</sub>) and analyzed by Wilcoxon rank test. A 2-sided probability of  $P < .05$  was used to determine significance. All statistical analyses were performed using JMP, version 10 (SAS Institute Inc., Cary, NC).

## RESULTS

The HIV-positive group consisted of 45 males and 3 females. The HIV-negative group consisted of 19 males and 3 females. There were no significant differences in median age (Q<sub>1</sub>, Q<sub>3</sub>) (HIV positive: 42 years [37, 50] vs HIV negative: 39 years [33, 41]), body mass index (HIV-positive: 24.2 kg/m<sup>2</sup> [22.9, 27.8] vs HIV negative: 25.1 kg/m<sup>2</sup> [23, 27.8]), nor current and/or former tobacco use between HIV-positive and HIV-negative groups (HIV-positive: 9 [18.8%] vs HIV-negative: 3 [13.6%]). All HIV-positive patients had an undetectable HIV RNA viral load, with a median CD4 count (Q<sub>1</sub>, Q<sub>3</sub>) of 465.5 copies/mL (296, 624). There were no differences between HIV-positive and HIV-negative groups in median systolic (HIV-positive: 116.5 mm Hg [110, 132.5] vs HIV-negative: 110.0 mm Hg [100, 116.5]) and median diastolic blood pressures (HIV-positive: 76 mm Hg [71.8, 80.5] vs HIV-negative: 76 mm Hg [68, 78.5]), and median heart rate (HIV-positive: 67 beats per minute [bpm], [58, 76.8] vs HIV-negative: 68 bpm [60, 72]). Symptoms of AD were present in 40% of HIV-positive compared with 9% of HIV-negative patients. The most common symptoms of AD reported by HIV-positive patients involved orthostatic intolerance, sleep problems; secretomotor issues such as abnormal sweating; pupillomotor problems such as light sensitivity and visual blurring; and male sexual dysfunction (Figure 1). The HIV-positive group demonstrated a significantly higher prevalence of patients experiencing symptoms of AD in 6 of the 11 domains compared with the HIV-negative group. The greatest difference was seen

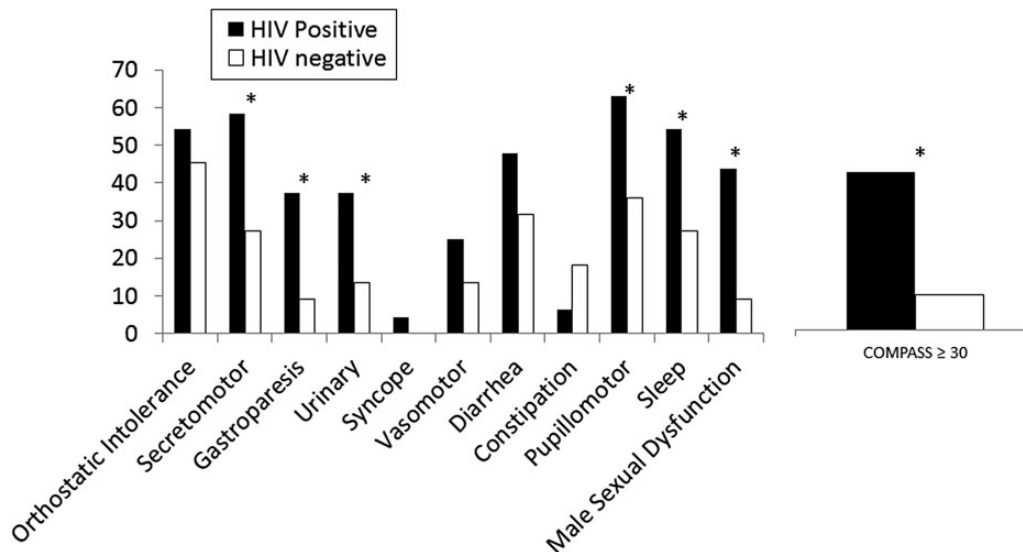
in male sexual dysfunction with 47% of HIV-positive patients experiencing symptoms, compared with 11% of the HIV-negative patients ( $P = .002$ ). Gastroparesis symptoms occurred in 37.5% in HIV-positive compared with 9.1% in HIV-negative patients ( $P = .015$ ). Secretomotor dysfunction was noted in 58% of the HIV-positive compared with 26% in HIV-negative patients ( $P = .016$ ). Pupillomotor, urinary, and sleep dysfunction were all higher in HIV-positive compared with HIV-negative patients (all  $P$  values  $< .05$ ). With all autonomic domain symptoms taken together, more HIV-positive patients (40%) had a COMPASS score  $\geq 30$ , which is suggestive of clinically significant autonomic neuropathy compared with HIV-negative patients (9%;  $P = .010$ ) (Figure 1).

Thirty-three HIV-positive patients underwent formal autonomic function testing. None of the HIV-negative patients had formal autonomic function testing. Among 33 HIV-positive patients, 27 (82%) had a CASS score above zero. Nineteen (58%) had evidence by CASS scores indicating mild autonomic neuropathy. Moderate autonomic neuropathy (ie, CASS = 4–6) was evident in 24% (8 of 33), but none had severe autonomic neuropathy (ie, CASS  $\geq 7$ ). A significant correlation was present between COMPASS and CASS ( $\beta = 4.892$ , standard error = 2.076,  $P = .025$ ).

## DISCUSSION

Our study found symptoms of AD prevalent in virologically suppressed HIV-positive patients on cART. The exact mechanism by which HIV modulates autonomic function is unknown [8]. It is hypothesized that HIV promotes a sympathetic imbalance, contributing to a virus-friendly Th1-biased immune environment [9]. Clinically, AD in HIV-positive patients is consistent as a spectrum of HIV-associated neuropathies [9, 10]. Pathologic studies involving the jejunal mucosa of HIV-positive patients demonstrates that damage to the autonomic nerve fibers occurs early in the course of HIV infection [11]. Using heart rate variability, Becker et al [12] demonstrated that cardiac AD gradually occurs with HIV disease progression.

Autonomic dysfunction in the era of cART appears to be mild [13]. Study participants demonstrated a median CASS score consistent with our previously reported findings [14]. Our study adds to the literature by highlighting symptoms of AD experienced by HIV-positive patients, and these symptoms can be elicited on routine visits. In the pre-cART era, severe AD was observed with debilitating postural hypotension, syncope, or cardiopulmonary arrest [15]. Syncope was not common in our study; however, orthostatic intolerance continues to be a prevalent along with a diverse range of symptoms involving the secretomotor, pupillomotor, gastrointestinal, and genitourinary systems.



**Figure 1.** Frequency of autonomic symptoms among human immunodeficiency virus (HIV)-infected patients compared with HIV-negative patients. \* $P < .05$   $\chi^2$  comparison between HIV-positive and HIV-negative groups. Abbreviation: COMPASS, composite automatic system scale.

Our study is strengthened by the exclusion of patients with diabetes mellitus, HCV infection, and drug/alcohol use, which are associated risk factors for autonomic neuropathy. The fewer comorbidities experienced by participants in our study may in part account for the lower median CASS score reported compared with those reported by Robinson-Papp [13]. Similar to the study by Robinson-Papp et al [13], the autonomic symptoms noted in our study were nonspecific in nature.

We recognize that our study has limitations. This is an observational study of a small, convenient sample of patients from a single clinic without formal autonomic testing in all participants. As a result of this sampling, a limitation is the small percentage of women. In addition, we excluded individuals with diabetes, HCV infection, and drug/alcohol use because these factors may confound the findings in autonomic neuropathy. This may limit the generalizability of our findings given the higher prevalence of diabetes, HCV infection, substance abuse, and alcoholism in the HIV-infected population. However, we wanted to determine the effects of HIV and its treatment on autonomic function. Although the study groups were similar, HIV-negative patients were not matched to study participants. Vitamin B12, folate, thyroid studies, and rapid plasma reagin were not performed on all patients. Other comorbidities such as renal impairment were not being taken into account, although the number of patients with significant metabolic and renal disease was small and unlikely to impact the study findings. Despite these limitations, our study did demonstrate significant symptoms of AD in a well characterized population of virologically suppressed HIV-positive patients.

## CONCLUSIONS

Human immunodeficiency virus-positive patients on suppressive cART have a higher prevalence of dysautonomia symptoms compared with HIV-negative patients. Further studies are needed to explore the prevalence, pathophysiology, clinical implication, and impact on quality of life of AD in HIV-positive patients on cART.

## Acknowledgements

We thank our study participants and community physicians for their roles in this study.

**Financial support.** This work was supported by the National Institutes of Health (grants K23 HL088981 [to D. C.], U54MD007584 [to B. K. N.], U54MD007584 [to C. M. S.], and U54MD007584 [to K. J. K.]).

The project was supported by the National Institute on Minority Health and Health Disparities (U54MD007584), National Institutes of Health (NIH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIMHD or NIH.

**Potential conflicts of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

## References

1. Montaner JS, Lima VD, Harrigan PR, et al. Expansion of HAART coverage is associated with sustained decreases in HIV/AIDS morbidity, mortality and HIV transmission: the “HIV Treatment as Prevention” experience in a Canadian setting. *PLoS One* **2014**; 9:e87872.
2. Robinson-Papp J, Sharma SK. Autonomic neuropathy in HIV is unrecognized and associated with medical morbidity. *AIDS Patient Care STDS* **2013**; 27:539–43.
3. Lee KA, Gay C, Portillo CJ, et al. Symptom experience in HIV-infected adults: a function of demographic and clinical characteristics. *J Pain Symptom Manage* **2009**; 38:882–93.

4. Shikuma CM, Seto T, Liang CY, et al. Vitamin D levels and markers of arterial dysfunction in HIV. *AIDS Res Hum Retroviruses* **2012**; 28:793–7.
5. Suarez GA, Opfer-Gehrking TL, Offord KP, et al. The Autonomic Symptom Profile: a new instrument to assess autonomic symptoms. *Neurology* **1999**; 52:523–8.
6. Weimer LH. Autonomic testing: common techniques and clinical applications. *Neurologist* **2010**; 16:215–22.
7. Newton JL, Okonkwo O, Sutcliffe K, et al. Symptoms of autonomic dysfunction in chronic fatigue syndrome. *QJM* **2007**; 100:519–26.
8. Rogers RC, Viard E, Hermann GE. CXCL12 sensitizes vago-vagal reflex neurons in the dorsal medulla. *Brain Res* **2013**; 1492:46–52.
9. Yun AJ, Lee PY, Bazar KA. Modulation of autonomic balance by tumors and viruses. *Med Hypotheses* **2004**; 63:344–51.
10. Boger MS, Hulgan T, Haas DW, et al. Measures of small-fiber neuropathy in HIV infection. *Auton Neurosci* **2012**; 169:56–61.
11. Griffin GE, Miller A, Batman P, et al. Damage to jejunal intrinsic autonomic nerves in HIV infection. *AIDS* **1988**; 2:379–82.
12. Becker K, Gorchach I, Frieling T, Haussinger D. Characterization and natural course of cardiac autonomic nervous dysfunction in HIV-infected patients. *AIDS* **1997**; 11:751–7.
13. Robinson-Papp J, Sharma S, Simpson DM, Morgello S. Autonomic dysfunction is common in HIV and associated with distal symmetric polyneuropathy. *J Neurovirol* **2013**; 19:172–80.
14. Chow D, Nakamoto B, So E, et al. Rates of autonomic dysfunction in HIV patients receiving antiretroviral therapy. *J Neurovirol* **2013**; 19:511–2.
15. Craddock C, Pasvol G, Bull R, et al. Cardiorespiratory arrest and autonomic neuropathy in AIDS. *Lancet* **1987**; 2:16–8.