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Chronic Distal Sensory Polyneuropathy Is a Major Contributor to Balance Disturbances in Persons Living With HIV

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Background: Medical comorbidities accumulate in older persons living with HIV (PLWH), causing disability and reduced quality of life. Sensory neuropathy and polypharmacy may contribute to balance difficulties and falls. The contribution of neuropathy is understudied.

Objective: To evaluate the contribution of chronic distal sensory polyneuropathy (cDSPN) to balance disturbances among PLWH.

Methods: Ambulatory PLWH and HIV− adults (N = 3379) were prospectively studied. All participants underwent a neurologic examination to document objective abnormality diagnostic of cDSPN and reported neuropathy symptoms including pain, paresthesias, and numbness. Participants provided detailed information regarding balance disturbance and falls over the previous 10 years. Balance disturbances were coded as minimal or none and mild-to-moderate. Covariates included age, HIV disease, and treatment characteristics and medications (sedatives, opioids, and antihypertensives).

Results: Eleven percent of participants reported balance disturbances at some time during the last 10 years; the rate in PLWH participants exceeding that for HIV− [odds ratio 2.59, 95% confidence interval: 1.85 to 3.64]. Fifty-two percent met criteria for cDSPN. Balance problems were more common in those with cDSPN [odds ratio = 3.3 (2.6–4.3)]. Adjusting for relevant covariates, balance disturbances attributable to cDSPN were more frequent among HIV+ than HIV− (interaction $P = 0.001$). Among individuals with cDSPN, older participants were much more likely to report balance disturbances than younger ones.

Conclusions: cDSPN contributes to balance problems in PLWH. Assessments of cDSPN in older PLWH should be a clinical priority to identify those at risk and to aid in fall prevention and the ensuing consequences, including bone fractures, subdural hematoma, hospital admissions, and fatal injury.

Key Words: HIV infection, aging, falls, neurology, everyday functioning

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INTRODUCTION

Falls are common among persons living with HIV (PLWH), particularly in those who are older, affecting 30% of those older than 50 years in a recent study.[1] They may have a profound impact on quality of life, disability, and health outcomes.[2] For example, balance problems interfere with the ability to benefit from physical exercise, which is strongly recommended to reduce cardiovascular risk, and for other health benefits.[3,4] In addition, falls increase the risk of fractures in PLWH who often have comorbid accelerated bone mineral density loss.[5] Self-reported balance disturbances represent an important, readily identifiable risk factor for future falls.[6] In PLWH, highly prevalent comorbidities and treatment factors are believed to contribute to balance disturbances and falls. These include peripheral neuropathy and polypharmacy.[2,3,7]

Objective loss of sensory function in the toes and feet on neurological examination are key features of chronic distal sensory polyneuropathy (cDSPN). Loss of afferent sensory signaling from the feet and legs due to neuropathy is a well-known cause of ataxia, balance disturbances, and falls. cDSPN is the most common type of peripheral neuropathy in PLWH, affecting half of those older than 50 years.[8] Virologic suppression on antiretroviral therapy does not eliminate cDSPN,[8,9] thus its prevalence remains high, particularly in older, long-term PLWH survivors.

As yet, no previous study has evaluated how cDSPN, defined by careful, objective neurological examination, impacts balance disturbances in PLWH. Previous reports

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have examined neuropathy defined only by the presence of neuropathic symptoms.[1] This is a critical distinction because more than half of cDSPN in HIV is asymptomatic. We aimed to evaluate the contribution of cDSPN to balance disturbances, relative to the impact of other comorbidities likely to affect balance, such as age, polypharmacy, and effectiveness of antiretroviral therapy. We hypothesized that balance disturbances would be much more common in PLWH compared to persons without HIV, and that cDSPN would be a strong, independent contributor to balance problems.

METHODS

Participants and Design

Participants were ambulatory HIV+ and HIV− adults enrolled in NIH-funded research protocols. They were enrolled at 6 sites (the University of California, San Diego; the University of Texas, Galveston; Johns Hopkins University; Washington University; the University of Washington and Mount Sinai) between September 11, 2003, and June 28, 2017. Each participant contributed data from a single baseline evaluation. The University's Institutional Review Board approved this study, and all participants provided written, informed consent.

Detailed information on the source populations and methods for these studies has been previously published.[8,10] Briefly, data were collected according to a standardized protocol of comprehensive neuromedical and laboratory assessments. Eligibility criteria included the ability to undergo neurologic examination to document objective abnormalities diagnostic of cDSPN and a structured clinical interview to provide details of neuropathy symptoms. General exclusion criteria for the study included blindness, wheelchair dependence, and falls known to be consequence of sustaining a violent blow, loss of consciousness, or sudden onset of paralysis as in stroke or epilepsy.

Clinical Evaluations

Physical Examination and Self-Reported Symptoms of cDSPN

cDSPN was diagnosed based on a standardized, objective neurological examination conducted by a trained clinician. cDSPN was defined by the presence of at least one specific sign: a consistent pattern of symmetrical, distal, bilateral reduction in deep tendon reflexes or reduced sensation to pin or vibration. cDSPN symptoms were self-reported pain (dysesthesia), tingling (paresthesia), and numbness (loss of sensation). In addition, gait was observed by the clinician; participants were asked to walk as briskly as could be done safely for 10–20 feet, turn, and return to the starting point, walking normally, on heels, toes, and in a tandem fashion. The predominant feature of the subject's gait pattern was recorded, ranging from normal gait, neuropathic or "foot slapping" (predominant abnormality is weakness of foot dorsiflexors), "waddling" (weakness of hip girdle muscles), ataxia (disproportionate difficulty with tandem), paraparesis (weakness with bilateral spasticity, scissoring), hemiparetic (unilateral weakness and spasticity), orthopedic (eg, knee, hip, or ankle pain, or limitation in range of motion), or mixed.

Self-Reported Balance Disturbance

A structured clinical interview was administered to participants by trained interviewers to collect any history of balance disturbance and its onset (the past few days up to the previous 10 years). Interexaminer reliability was ensured through systematic training. Balance disturbances were classified as not present; occasionally unsteady, no falls; frequently unsteady; some near-falls or rare falls; and must use a cane, walker, or other prop. We recoded balance disturbance classes into minimal or none (occasionally unsteady, no falls) and mild-to-moderate (frequently unsteady, some near-falls, some falls, or must use a cane, walker, or other prop).

HIV Characteristics and Covariates

The following HIV disease and treatment data were obtained: estimated duration of HIV infection, nadir $CD4^+$ lymphocyte counts, AIDS status, and current use of cART. Laboratory assays included CD4 and viral load. Data on use of antihypertensive and other medications, including sedatives and opioids, and body mass index were obtained to examine as potential covariates.

Statistical Analysis

Associations of polyneuropathy and HIV status with balance disturbance were analyzed with Fisher exact test. Confidence intervals (CIs) for point estimates of frequency were calculated by using the Wilson procedure with a correction for continuity. Covariates were evaluated with logistic regression. Multivariable analyses were adjusted for age, sex, GDS impairment, sedatives, nadir CD4, duration of HIV infection, viral load, and use of antihypertensive, sedatives, and/or opioid medications. Statistical analyses were performed using JMP Pro13 and R statistical software (version 3.4.1).

RESULTS

Demographic and Clinical Characteristics

Participants were 2647 HIV+ and 732 HIV− adults with a mean age of 45.5 years (SD = 11 years). PLWH were on average 1 year older ($P = 0.036$) and more likely to be men ($P < 0.0001$) and African American ($P < 0.0001$) than HIV− participants (Table 1).

Relationship Between cDSPN, Neuropathic Symptoms, and Balance Disturbance

Overall, 385 participants [11.3%; (95% CI: 10.3 to 12.5)] reported some balance disturbance during the previous 10 years. The proportion that used a walker, cane, or other prop was 3.4% (2.8–4.1). Balance disturbances were more common in HIV+ than HIV− participants (13.0% vs 5.5%, odds ratio [OR] = 2.59, 95% CI: 1.85 to 3.64). cDSPN was present in 52% (50.5–53.9) of the participants and was

TABLE 1. Population Characteristics According to HIV Serostatus, Using Welch T-Test for Normally Distributed Continuous Variables, the Wilcoxon Rank–Sum Test for Non-normal Data, and Fisher Exact for Categorical Variables

Variable	HIV+ (n = 2647)	HIV− (n = 732)	Effect Size (95% CI)	*P*
Age (yr), mean (SD)	45.8 (10.5)	44.8 (13.9)	0.09 (0 to 0.17)*	0.038
Education (yr), mean (SD)	12.9 (3.26)	13.6 (4.08)	−0.19 (−0.27 to −0.11)*	<0.001
Male, n (%)	2147 (81.1)	484 (66.1)	2.2 (1.83 to 2.65)†	<0.001
Ethnicity, n (%)				<0.001
Non-Latino white	1215 (45.9)	410 (56.0)		
African American	894 (33.8)	134 (18.3)		
Latino	452 (17.1)	143 (19.5)		
Other	66 (2.49)	32 (4.37)		
Asian	20 (0.76)	13 (1.78)		

*Effect size presented as Cohen's d.
†Effect size presented as odds ratio.

symptomatic (pain, paresthesias, or numbness) 41.6% (39.9–43.3). cDSPN was more frequent among PLWH (59.4%) compared to those without HIV-1 infection (26.0%; OR = 4.18, 95% CI: 3.48 to 5.02). Adjusting for demographic differences (age, sex, and race/ethnicity) between PLWH and HIV− participants did not substantially alter the ORs [95% CI] for balance disturbances (2.67 [2.05 to 3.49]) or for cDSPN (5.36 [4.33 to 6.66]). Table 2 shows demographics and HIV disease and treatment characteristics according to the presence of balance disturbance. Individuals experiencing balance disturbance were significantly older and more likely to be women, had higher BMI, and were more likely to be of non-Latino white race/ethnicity than those who did not report balance disturbance. Among HIV+ individuals, those with balance disturbances had lower CD4 nadir, longer estimated duration of HIV infection, and increased use of antihypertensives, opioids, and sedatives.

As seen in Table 3, results showed a significant increase in the risk of balance disturbances in participants with cDSPN. More severe cDSPN conferred a greater risk of balance difficulties: The odds of balance disturbances increased from mild cDSPN (only 1 abnormal sign; OR = 2.45, 95% CI: 1.82 to 3.28) to moderate cDSPN (≥2 signs; OR = 5.45, 95% CI: 4.11 to 7.11). cDSPN was associated with both minimal (OR = 1.91, 95% CI: 1.57 to 2.34) and mild–moderate (OR = 3.08, 95% CI: 2.46 to 3.84) balance difficulties. The onset of the preponderance of the self-reported balance disturbances was within the past year (28%) or 1–10 years (58%). Limiting balance disturbances to those with reported onset in the past year, cDSPN was still associated with a significantly higher frequency of balance disturbances (51% vs 30%; $P = 0.0014$). Self-reported neuropathic symptoms (pain, paresthesia, and loss of sensation) also were significantly associated with balance disturbances. ORs for mild–moderate balance disturbance in persons with relative to without neuropathic symptoms were 1.81 (95% CI: 1.68 to 1.96, pain), 2.23 (95% CI: 2.01 to 2.48, paresthesia), and 2.04 (95% CI: 1.87 to 2.22, loss of sensation).

Gait examination by the clinician revealed an abnormal ataxic pattern in 4.3% (3.6–5.0) of participants, with other abnormal patterns in 4.4% (3.8–5.2). Clinical ataxia was more common in those who self-reported balance disturbance (13.0%), compared with those who did not (3.1%; OR = 4.62 95% CI: 3.26 to 6.57).

The frequencies of current opioid, antihypertensive medication, and sedative use among PLWH were 14.5% (13.3–15.7), 7.8% (6.9–8.9), and 11.2% (10.2–12.3), respectively. ORs for mild–moderate balance disturbance in persons with relative to without medication use were 3.02 (95% CI: 2.37 to 3.85) for opioids, 1.73 (95% CI: 1.23 to 2.42) for antihypertensives, and 1.82 (95% CI: 1.37 to 2.43) for sedatives. Current opioid use was common in individuals with cDSPN (OR = 2.28, 95% CI: 1.89 to 2.77), particularly those who reported neuropathic pain (OR = 3.37, 95% CI: 2.77 to 4.09).

cDSPN and History of Balance Disturbance

Among all study participants, those with cDSPN were 3 times more likely to have reported balance problems in the preceding 10 years (OR = 3.30, 95% CI: 2.55 to 4.28). After adjusting for HIV serostatus, age and sex, as well as sedative and antihypertensive and opioid use, the OR for DSPN remained significant (OR = 2.07, 95% CI: 1.57 to 2.73). A sensitivity analysis showed that removing individuals who used a cane, walker, or other prop did not substantially alter the findings (OR = 2.86, 95% CI: 2.16 to 3.78). Participants with symptomatic cDSPN (1 or more symptoms) were nonsignificantly more likely than those with asymptomatic cDSPN to report balance disturbances (OR = 5.18, 95% CI: 4.07 to 6.59 vs OR = 3.15, 95% CI: 2.09 to 4.74).

Logistic regression models were run to examine whether HIV serostatus, age, and sex impacted the relationship between cDSPN and balance disturbance. A significant interaction between HIV serostatus and the presence of cDSPN was observed, such that balance disturbances attributable to cDSPN were more frequent among HIV+ than HIV− (Fig. 1; interaction *P*-value = 0.007) after controlling for relevant covariates [age, HIV disease, and treatment

TABLE 2. Population Characteristics According to Presence or Absence of Balance Disturbance, Using Welch T-Test for Normally Distributed Continuous Variables, the Wilcoxon Rank–Sum Test for Non-normal Data, and Fisher Exact for Categorical Variables

Variable	Mild–Moderate Balance Disturbance (n = 385)	Minimal or No Balance Disturbance (n = 2994)	Effect Size (95% CI)	*P*
Demographics				
Age (yr), mean (SD)	51.9 (10.6)	44.7 (11.2)	0.68 (0.57 to 0.78)‡	<0.001
Education (yr), mean (SD)	13.1 (2.98)	13.1 (3.52)	0 (−0.11 to 0.11)‡	0.99
Male, n (%)	278 (72.2%)	2353 (78.6%)	0.71 (0.55 to 0.91)§	0.006
Ethnicity, n (%)				0.006
Non-Latino White	197 (51.2%)	1428 (47.7%)		
African American	127 (33.0%)	901 (30.1%)		
Latino	47 (12.2%)	548 (18.3%)		
Other	10 (2.60%)	88 (2.94%)		
Asian	4 (1.04%)	29 (0.97%)		
BMI, mean (SD)*	28.0 (7.15)	26.9 (9.69)	0.16 (0.05 to 0.27)‡	0.004
HIV disease and treatment characteristics				
HIV status, n (%)	345 (89.6%)	2302 (76.9%)	2.59 (1.84 to 3.73)§	<0.001
AIDS status, n (%)	254 (73.6%)	1399 (60.8%)	1.8 (1.39 to 2.35)§	<0.001
CD4 current (cells/uL), median (IQR)†	490 (282, 706)	471 (302, 687)	0 (−0.11 to 0.12)‡	0.95
CD4 nadir (cells/uL), median (IQR)†	116 (23, 245)	172 (41, 300)	−0.21 (−0.32 to −0.09)‡	<0.001
Plasma viral load undetectable, n (%)	177 (58.2%)	1252 (58.8%)	1.02 (0.79 to 1.31)§	0.85
cART (currently using), n (%)	292 (84.9%)	1840 (80.0%)	1.4 (1.02 to 1.95)§	0.034
Duration of infection (yr), mean (SD)	14.5 (13.6)	11.5 (11.0)	0.23 (0.11 to 0.34)‡	<0.001
Other medication use (n, %)				
Antihypertensives (currently using), n (%)	33 (9.57%)	169 (7.34%)	1.33 (0.87 to 1.99)§	0.16
Sedatives (currently using), n (%)	58 (16.8%)	280 (12.2%)	1.46 (1.05 to 2)§	0.019
Opiates (currently using), n (%)	107 (31.0%)	331 (14.4%)	2.68 (2.05 to 3.48)§	<0.001

*log10 transformed prior to analysis.
†Square root transformed before analysis.
‡Effect size presented as Cohen's d.
§Effect size presented as odds ratio.

characteristics and medications (sedatives, opioids, and antihypertensives)].

The prevalence of balance disturbances in women was higher than in men (14% vs 10%; $P = 0.0045$). This was true regardless of HIV serostatus (for HIV− women, OR = 2.14, 95% CI: 1.04 to 4.31; for HIV+ women, OR = 1.81, 95% CI: 1.31 to 2.50). The interaction between sex and cDSPN also was significant (Fig. 2; interaction P-value = 0.027) such that balance disturbances were proportionately more common in men with cDSPN than in women with cDSPN. Controlling for relevant covariates did not substantially alter the findings. Among all participants, balance disturbances were more frequent in older vs younger participants [OR 1.42 (1.26 to 1.59) per 10-year increase in age]; the interaction term was not significant ($P = 0.77$). Results were similar for the HIV+ subgroup.

DISCUSSION

We found that PLWH as compared with HIV-uninfected individuals were 3 times more likely to report balance difficulties and 4 times more likely to have cDSPN. The prevalence of cDSPN in our cohort was high; similarly, high prevalence has been reported in other studies.[13] PLWH were particularly susceptible to balance problems attributable to cDSPN. Our findings were robust to consideration of covariates including demographics and polypharmacy. Despite the importance and high prevalence of neuropathy and its known causal connection to balance disturbances in conditions other than HIV, this link in PLWH is understudied.

A major strength of our study is that we assessed the association of cDSPN with HIV disease in a large, prospectively assembled sample in which all participants underwent a standardized objective examination for

TABLE 3. Odds Ratio for Mild-To-Moderate Balance Disturbance in Persons With Relative to Without cDSPN Signs and Symptoms, Using Fisher Exact Test

cDSPN Signs	OR	95% CI
≥ 2 signs	5.45	4.11 to 7.11
1 sign	2.45	1.82 to 3.28
cDSPN symptoms		
Pain	1.81	1.68 to 196
Paresthesia	2.23	2.01 to 2.48
Loss of sensation	2.04	1.87 to 2.22

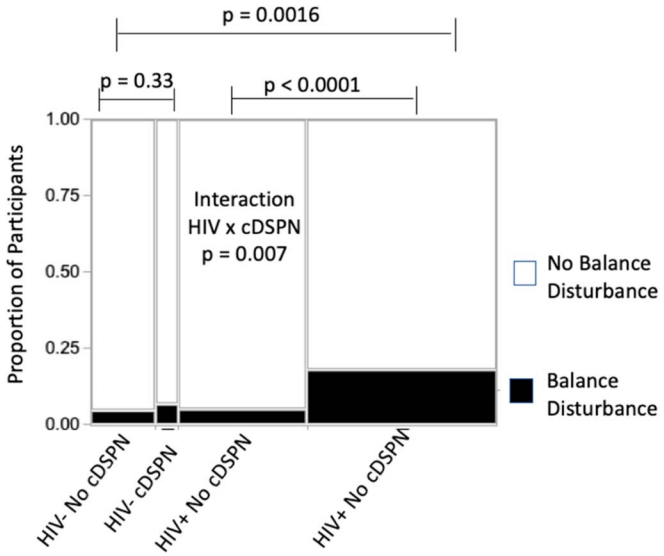

FIGURE 1.

polyneuropathy. Participants were derived from multiple studies with sites across the United States, enhancing representativeness. The large sample size provided sufficient power to adjust for multiple comorbidities.

We found that self-reported balance disturbances were associated with a higher frequency of gait ataxia on objective clinical examination. However, only a small proportion of PLWH reporting balance disturbances had frank gait ataxia on gait examination. Although other interpretations are possible, we favor the view that the clinical examination is relatively insensitive to balance disturbances and is particularly likely to miss difficulties that are intermittent or subtle. Both objective ataxia on neurological examination and self-reported balance disturbances[11] are predictive of falls.

Previous research[1] found that the odds of falling increased by 1.7 for PLWH with neuropathy, whereas in our study, the odds of balance disturbances increased by 3 for individuals with cDSPN. Several methodological factors may account for the differences between the 2 studies. We assessed the presence of polyneuropathy using a previously validated objective neurological examination, while the previous study used subjective participant reports of neuropathy symptoms. We considered a prospectively collected 10-year history of falls and imbalance, whereas the aforementioned study assessed only recent fall history (past 12 months). Another difference between our study and previous work is the focus on sensory neuropathy. By comparison, Gewandter et al[12] showed that in cancer survivors with chemotherapy-induced peripheral neuropathy, falls were significantly associated with motor neuropathy.

Previous research[1,2,6,7] found significant risk factors for falls in HIV included female sex, diabetes, antidepressants, sedatives, opioids, didanosine use, exhaustion, weight loss, and balance problems (all OR ≥ 2.5; $P \leq 0.05$). We similarly found that balance disturbances were more common in women than men and in participants taking sedatives, opioids, and antihypertensives compared with those not on these medications.

Our study has several limitations. The definition of balance disturbances included individuals who used a cane, walker, or other prop. Some of these may have used a prop due to orthopedic reasons such as hip or knee pathology, rather than balance difficulties. However, the proportion using a prop was relatively small, and in a sensitivity analysis, removing these individuals did not substantially alter the findings. Participants had to be able to visit the research center, implying that they were relatively healthy. Underrepresentation of less healthy individuals may have resulted in an underestimation of the impact of cDSPN on balance disturbances.[9] To assess whether the relationship between cDSPN and balance disturbances might be causal, it would be helpful to know their temporal ordering, specifically, whether cDSPN preceded balance disturbances. In this cross-sectional study, it was not possible to assess temporal ordering because the balance disturbances were reported retrospectively, whereas cDSPN was ascertained prospectively. Patient-reported symptoms cannot be used to estimate the date of onset of cDSPN because the condition is asymptomatic in more than 50% of cases. Nevertheless, we believe that cDSPN likely preceded and contributed substantially to balance disturbances for several reasons. First, cDSPN in HIV is a chronic condition, typically present for many years before it is evaluated. It is reasonable to expect that cDSPN was present for some months or years before the clinical examination performed in this study. Furthermore, the potential causal connection between loss of afferent sensory function in cDSPN and balance disturbances is plausible and has been demonstrated in other patient populations.

We observed a relatively high prevalence of cDSPN in our HIV− cohort, suggesting that the cohort may not be representative of the general population. We believe this relatively high prevalence is likely due to the fact that HIV− participants were selected to have risk factors similar to the HIV+ sample, such as histories of alcohol abuse (27%) and IV drug use, some of which may influence the prevalence of

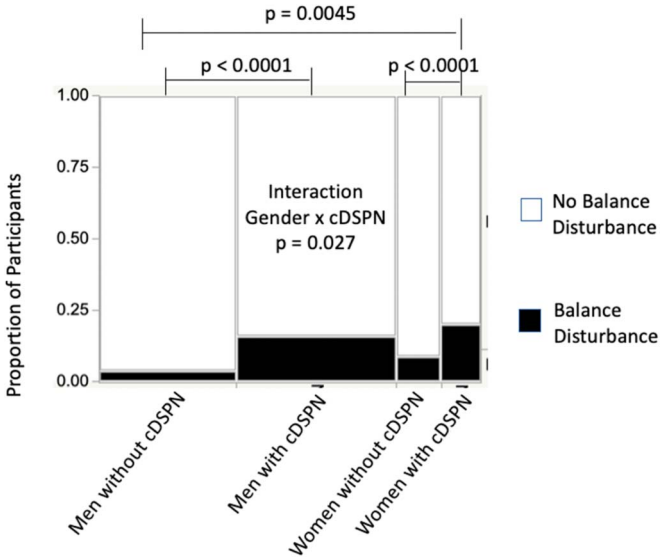

FIGURE 2.

neuropathy. They also had comorbidities such as diabetes mellitus (7%), a risk factor for neuropathy, and overweight/obesity. A limitation of many previous studies of HIV− individuals is that they defined neuropathy on the basis of symptoms alone, rather than clinical examination. This approach is likely to produce substantial underestimates of prevalence because cDSPN is frequently asymptomatic. Some previous studies have found HIV− individuals to have a prevalence of cDSPN similar to that found in our report. For example, the prevalence of peripheral neuropathy was 29% among subjects at risk for diabetes mellitus with an average age of 53 years[14]

Because of the cross-sectional design of our study, we were not able to investigate causal relationships between polyneuropathy and HIV disease. However, the causal relationship is intuitively plausible and supported by previous research, and it survived evaluation of important covariates. In our study, we associated cDSPN with HIV disease. These associations were independent of age, sex, and diabetes mellitus. Factors not directly assessed in this study may contribute to balance disturbance. However, we excluded data from participants affected by many of these conditions, including blindness, and balance disturbances known to be consequence of sustaining a violent blow, loss of consciousness, or sudden onset of paralysis as in stroke or epilepsy. Other conditions such as knee or hip arthritis and vestibular disorders are often associated with balance disturbance. These conditions may, in turn, be more common among those with cDSPN, confounding the association with it.

In conclusion, chronic polyneuropathy is a disabling disorder that causes significant disability by itself[10] and leads to additional morbidity by exacerbating fall risk. cDSPN is frequently asymptomatic, meaning that recognition requires neurological examination.[8] The examination for cDSPN requires 2–3 minutes and substantially enhances the detection of those at risk for falls. Previous studies have demonstrated that physical therapy and physical exercise, particularly gait training, are effective in preventing future falls.[3,4] An important issue for future studies to address is whether objective evidence of cDSPN and self-reported balance disturbances predict preventable falls in PLWH prospectively followed.

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