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Characteristics of Motor Dysfunction in Longstanding Human Immunodeficiency Virus

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Background. Cognitive dysfunction in human immunodeficiency virus (HIV) has decreased, but milder forms of HIV-associated neurocognitive disorders (HAND) persist along with motor dysfunction. The HIV Motor Scale (HMS) is a validated tool that captures motor abnormalities on routine neurologic examination and which is associated with cognitive impairment in HIV. In this study, we applied a modified HMS (MHMS) to a nationwide cohort of people with longstanding HIV to characterize and understand the factors contributing to motor dysfunction.

Methods. The National NeuroAIDS Tissue Consortium is a nationwide longitudinal cohort study. Participants undergo regular assessments including neurological examination, neuropsychological testing, and immunovirologic data collection. Data from examinations were used to calculate the MHMS score, which was then correlated with history of AIDS-related central nervous system (CNS) disorders (ARCD; eg, prior CNS opportunistic infection), cerebrovascular disease (CVD), and HAND.

Results. Sixty-nine percent of participants showed an abnormality on the MHMS, with 27% classified as severe. Results did not vary based on demographic or immunologic variables. The most common abnormalities seen were gait (54%), followed by coordination (39%) and strength (25%), and these commonly co-occurred. CVD ($P = .02$), history of ARCD ($P = .001$), and HAND ($P = .001$) were all associated with higher (ie, worse) HMS in univariate analyses; CVD and ARCD persisted in multivariate analyses. CVD was also marginally associated with symptomatic HAND.

Conclusions. Complex motor dysfunction remains common in HIV and is associated with CVD, ARCD, and to a lesser extent, HAND. Future studies are needed to understand the longitudinal trajectory of HIV-associated motor dysfunction, its neural substrates, and impact on quality of life.

Keywords. HIV; neurocognitive disorders; cerebrovascular disease; motor dysfunction.

Cognitive dysfunction in human immunodeficiency virus (HIV), first described in the 1980s as a progressive deterioration in cognition along with central nervous system (CNS) motor and behavioral disturbances [1], was initially estimated to occur in up to two-thirds of people with AIDS [2, 3]. With the introduction of combination antiretroviral therapy (cART), the overall prevalence and severity of cognitive dysfunction declined [4, 5], prompting the creation of the Frascati criteria, which define 3 HIV-associated neurocognitive disorders (HAND): asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD) [6]. However, even given these milder HAND phenotypes, CNS motor dysfunction persists in the cART era and may worsen over time [7–13]. This complex HIV-associated motor dysfunction includes pyramidal, extrapyramidal, and cerebellar features, and can be quantified by the HIV Motor Scale (HMS), a validated tool that captures motor abnormalities detectable on routine neurologic examination, and which is associated with cognitive impairment in HIV [14]. Quantifying motor dysfunction is important given its role in neurological disorders of aging [15–17] and its impact on a person's ability to age successfully and maintain independence [18–20]. Motor dysfunction is also a significant component of frailty, which is a clinical syndrome featuring weakness, slowed walking, and low physical activity. Frailty predicts disability in older adults [21]; within HIV cohorts, frailty correlates inversely with survival and successful cognitive aging [22–24].

With many patients entering their third and even fourth decades of HIV infection, comorbidities such as cerebrovascular disease (CVD) are increasing [25, 26], occurring on a background of aging, the inflammatory effects of chronic viral infection, long-term use of cART, and in some cases a prior history of

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AIDS-related CNS disorders (ARCDs). These factors are likely important contributors to CNS motor dysfunction in HIV. In particular, CVD is known to cause motor slowing and predict cognitive impairment in non-HIV patient populations [27, 28], as well as in people living with HIV (PLWH) [7].

In the present study, we sought to use a modified HMS (MHMS) to describe motor impairment in the National NeuroAIDS Tissue Consortium (NNTC) [29–31], a nationwide cohort of medically complex individuals with longstanding HIV. We also sought to understand the factors that may be contributing to motor dysfunction in this cohort, including HAND, ARCD, CVD, demographic factors, and immunovirologic parameters.

METHODS

Study Participants

The NNTC is comprises 4 clinical sites (Galveston, Texas; Los Angeles, California; New York City, New York; San Diego, California) and central data coordinating centers (University of Nebraska; The Emmes Company). The NNTC is a longitudinal cohort and organ donation study established in 1998 with a mission to serve as a research resource of neurologic and other tissues samples from deeply phenotyped PLWH. All shared NNTC study procedures are conducted according to a common protocol, which is approved by each site's local institutional review board. All participants provide written informed consent. The primary inclusion criterion for the NNTC is willingness to be an organ donor upon death. In addition, the study seeks to enroll PLWH with higher mortality risk, for example, those with greater burden of comorbid medical illness and/or older age. For the purposes of this analysis, all participants in the NNTC who had neurologic examinations between August 2017 and March 2019 were included. For participants who were evaluated more than once during this interval, the most recent evaluation was used.

Study Assessments

Participants are evaluated at 6-, 12-, or 24-month intervals based on a clinical judgment, with more stable participants being evaluated less frequently. Immunovirologic data collection includes current and nadir CD4 T-cell count, plasma HIV RNA, current cART, HIV disease duration, and risk factor for HIV acquisition. Medical and neurological history is collected from participants using standardized forms by medically experienced staff (typically a research nurse). This includes the presence of musculoskeletal disorders (eg, arthritis, spinal pain, avascular necrosis of the hip, and prior musculoskeletal injury or surgery) that could contribute to motor dysfunction.

A comprehensive neurologic examination is performed by a neurologist or other trained healthcare provider (registered nurse, nurse practitioner, or physician). This includes assessment of neurologic function in the following standard domains: cranial nerves, strength, deep tendon reflexes, motor tone and strength, sensory function, coordination, and gait. These data (with the exception of cranial nerves and sensory function) are then used to calculate the MHMS, which includes 5 subscores: gait, coordination, strength, tone, and reflexes (tone and reflexes are only coded as abnormal if they are increased, ie, indicative of CNS dysfunction). The MHMS differs from the original [14] in that it excludes pathologic reflexes (ie, snout, glabellar, and Babinski signs), which are not routinely collected by all NNTC sites. The resultant MHMS is a continuous measure on a scale of 0–18 (instead of 0–20; see Appendix for scoring), which can also be categorized as follows: 0 = normal; 1–4 = mild impairment; ≥5 = severe impairment. Participants are also assigned a diagnosis of distal symmetric polyneuropathy (DSP) if they have at least 2 of 3 signs on neurologic examination (decreased/absent: distal vibration sensation, distal sharp sensation, ankle reflexes). DSP is further designated as asymptomatic or symptomatic, with symptomatic disease classified as mild, moderate, severe, or incapacitating.

Standardized study-specific algorithms (which include consideration of the neurologic examination and data from the medical history) are used to assess participants for the following ARCDs (including active disease or, more commonly, residual deficits from prior disease): primary CNS lymphoma, cerebral toxoplasmosis, progressive multifocal leukoencephalopathy, cryptococcal meningitis, cytomegalovirus encephalitis, CNS tuberculosis, and neurosyphilis. A standardized study-specific algorithm is also used to assign a diagnosis of CVD, which is defined as the presence of 1 or more of the following: (1) patient-reported sudden-onset focal neurologic event deemed most likely to represent a CNS vascular event; (2) chart documentation of CVD; (3) evidence of a prior parenchymal infarct or hemorrhage on clinical neuroimaging; (4) clinical neuroimaging findings interpreted as consistent with small vessel ischemic changes.

The NNTC neuropsychological test battery has been previously described [32] and includes tests of the following domains: learning, memory, abstraction/executive functioning, speed of information processing, verbal fluency, working memory, and motor function. Global and domain-specific T scores are calculated and used to derive clinical ratings. Cognitive diagnoses are assigned by study neuropsychologists and include the following: normal, ANI, MND, HAD, and neuropsychologic impairment likely due to other (non-HIV) causes (NPIO).

Statistical Analysis

Descriptive statistics were used to understand the prevalence of motor abnormalities in the sample, and Spearman rank-order correlation was used to quantify correlations between the presence of abnormalities in each of the HMS subscores. Univariate and multivariate associations with the MHMS were modeled using a negative binomial distribution (SAS procedure

GENMOD, version 9.4) with the MHMS as a continuous variable. Univariate associations were sought between the MHMS and the following: CVD, ARCD, and cognitive diagnosis (normal, ANI, MND, HAD, NPIO). In addition, the following potential covariates/confounders for motor dysfunction were considered: age, race/ethnicity, sex, presence of a musculoskeletal disorder, intravenous drug use vs sexual risk factor for HIV acquisition, history of alcohol use disorder, current and nadir CD4 T-cell count, HIV disease duration, current plasma HIV RNA, current use of integrase inhibitors, current use of protease inhibitors, current use of nonnucleoside reverse transcriptase inhibitors, number of nucleoside reverse transcriptase inhibitors, and study site. We also included the presence of DSP with at least moderate symptoms (referred to hereafter as symptomatic DSP) as a covariate due to the potential for painful DSP to interfere with gait (which is one of the domains of the MHMS). Univariate and multivariate associations with the presence of an abnormality in the individual subscores were modeled using logistic regression (SAS procedure LOGISTIC, version 9.4).

For all analyses, factors significant at $P < .10$ in univariate analysis were retained for multivariable models. In the multivariable model, factors were removed via backward elimination until all remaining factors were statistically significant at $P < .05$. Incidence rate ratios (IRRs) or odds ratios (ORs) with 95% confidence intervals (CIs) were computed as appropriate. Analyses were not adjusted for multiple comparisons.

RESULTS

Participant Characteristics

A total of 354 participants were included (Table 1). The study population was demographically diverse with ample representation of African American, Hispanic/Latino, and white race/ethnicity; the proportion of women was representative of the US population of PLWH. HIV infection was typically longstanding with significant past immunocompromise and subsequent sustained immune reconstitution.

Table 1. Participant Characteristics

Characteristic	Mean (SD) or %
Age, y, mean (SD)	59.6 (9.1)
Sex, %	
Male	73
Female	27
Race, %	
African American	38
White	51
Other/unknown	11
Ethnicity, %	
Hispanic/Latino	33
Non-Hispanic/Latino	67
Current $CD4^+$ count, cells/μL, mean (SD)	538 (304)
Nadir $CD4^+$ count, cells/μL, mean (SD)	124 (178)
Duration of known HIV infection, y, mean (SD)	24 (8)
HIV viral load, %	
≤50 or undetectable	82
51–999	10
≥1000	7
Current cART regimen, %	
Integrase-containing regimen	72
Protease inhibitor–containing regimen	34
NNRTI-containing regimen	23
Not on cART	4

Abbreviations: cART, combination antiretroviral therapy; HIV, human immunodeficiency virus; NNRTI, nonnucleoside reverse transcriptase inhibitor; SD, standard deviation.

Motor and Neurocognitive Dysfunction and CNS Comorbidities

Overall, motor dysfunction was common (Figure 1), with 69% of participants displaying some abnormality on the MHMS and 27% being in the severe range; the range of observed MHMS was 0–17, with a median of 2 (interquartile range [IQR], 0–5). Of note, the properties of the MHMS were very similar to the HMS. The full HMS was available for a subset of participants (n = 211), in whom the MHMS and HMS were very highly correlated overall ($r = .99$, $P < .001$), and identical in 74%.

Abnormalities in each subscore of the MHMS (strength, reflexes, coordination, gait, and tone) were present, with gait abnormalities being most common (54%) followed by coordination (39%), strength (25%), reflexes (24%), and tone (12%). Abnormalities across subscores often occurred together; among the 244 participants who displayed an abnormality in 1 subscore, the majority (66%) displayed abnormalities in at least 1 other subscore, with the median number of abnormal subscores being 2 (IQR, 1–3). This tendency for multiple abnormalities to occur together was reflected by statistically significant bivariate correlations between all individual subscores (Table 2). The 3 most commonly abnormal subscores (gait, coordination, and strength) were also among the most strongly correlated. Thirty-six percent of the sample was cognitively normal, with ANI in 16% and symptomatic cognitive impairments in 42% (Table 3). Given the medical complexity of our cohort, CNS disease was relatively common: 28% carried a diagnosis of CVD and 7% had a prior ARCD (there were no participants with active ARCD).

Correlates of Motor Dysfunction (Univariate)

Cerebrovascular disease ($P = .02$), history of ARCD ($P = .001$), and HAND ($P = .001$) were all associated with higher (ie, worse) MHMS in univariate analyses. Among participants classified as neurocognitively normal, 54% had motor impairment compared to 79% among participants with HAND (71% in ANI, 79% in MND, 86% in HAD, and 85% in NPIO). In keeping with this finding, poorer overall cognitive performance as measured by lower global T scores was also associated with higher MHMS ($P = .02$). The neurocognitive domains individually associated with MHMS were motor ($P < .001$), speed of information processing ($P < .001$), verbal fluency ($P = .02$), and working memory ($P = .04$).

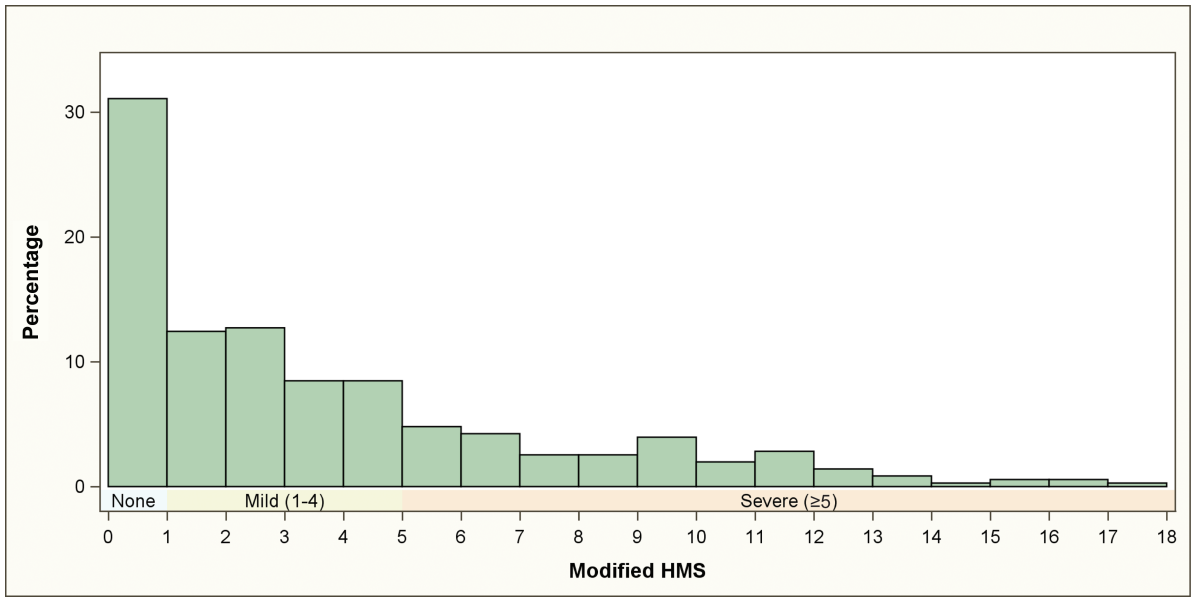

Figure 1. Histogram demonstrating the distribution of motor scores. Zero is normal, 1–4 is mildly abnormal, and ≥5 is severely abnormal. Abbreviation: HMS, Human Immunodeficiency Virus Motor Scale.

Abstraction/executive function was marginally associated with MHMS ($P = .09$), while learning and memory were not ($P > .1$).

Cerebrovascular disease was marginally associated with a symptomatic HAND diagnosis ($P = .05$). Among participants classified with normal cognition or ANI, rates of CVD were 25% and 21% respectively, whereas participants with symptomatic cognitive impairment all had rates of CVD ≥30% (30% in MND, 39% in HAD, 35% in NPIO). As expected, the presence of symptomatic DSP was associated with an abnormal gait subscore ($P = .007$) as well as the MHMS overall ($P = .0004$).

Demographic, musculoskeletal, alcohol use, and immunovirologic variables were not associated with the MHMS ($P > .05$ for all). Participants from the Los Angeles site, on average, had higher MHMS scores and a higher rate of abnormality in every subscore compared to the other sites ($P < .001$). There was no immediately obvious reason for this, although the Los Angeles site also had higher rates of cognitive impairment (20% normal at Los Angeles vs 33%–59% normal at the other sites) and more Hispanic/Latino participants (50% at the Los Angeles site vs 18%–32% at the other sites).

Table 2. Bivariate Spearman Rank Correlations Between Abnormalities in the Modified Human Immunodeficiency Virus Motor Scale Subscores

Scale	Correlation Coefficient	*P* Value
Coordination and gait	0.41	<.0001
Coordination and strength	0.35	<.0001
Gait and strength	0.35	<.0001
Reflexes and tone	0.35	<.0001
Strength and tone	0.27	<.0001
Coordination and tone	0.23	<.0001
Gait and reflexes	0.22	<.0001
Gait and tone	0.21	<.0001
Coordination and reflexes	0.17	.0014
Reflexes and strength	0.16	.0029

Correlates of Motor Dysfunction (Multivariate Results)

We controlled for site of participation (IRR for each site vs Los Angeles site, 0.48–0.49; P <.0001 to .001) and the grooved pegboard T score, which constitutes the motor domain of our neuropsychologic test battery (IRR, 0.97 [95% CI, .96–.98]; $P < .0001$), the former because of the variability between sites and the latter because as part of the data used to establish the

Table 3. Prevalence of Central Nervous System Diagnoses

	%
Neurocognitive Diagnosis	
Normal	36
Asymptomatic neurocognitive impairment	16
Minor neurocognitive disorder	16
HIV-associated dementia	8
Neuropsychological impairment due to other cause	18
No diagnosis assigned	6
AIDS-related CNS disorders	
Cerebral toxoplasmosis	3
Cryptococcal meningitis	2
Progressive multifocal leukoencephalopathy	2
Neurosyphilis	1
Cytomegalovirus encephalitis	<1
CNS tuberculosis	<1
Primary CNS lymphoma	0
History of any AIDS-related CNS disorder	7
Cerebrovascular disease	28

Abbreviations: CNS, central nervous system; HIV, human immunodeficiency virus.

Table 4. Multivariate Associations With the Modified Human Immunodeficiency Virus Motor Scale

Parameter	Comparison	IRR (95% CI)	*P* Value
Site	Texas (vs Los Angeles)	0.49 (.33–.74)	.0006
	San Diego (vs Los Angeles)	0.49 (.31–.76)	.001
	New York (vs Los Angeles)	0.48 (.35–.65)	<.0001
CVD	Presence (vs absence)	1.57 (1.16–2.13)	.003
ARCD	Presence (vs absence)	1.86 (1.17–2.98)	.009
DSP	DSP with at least moderate symptoms (vs DSP with no or mild symptoms, or no DSP)	1.67 (1.27–2.20)	.0002
Pegboard dominant hand T-score	Continuous	0.97 (.96–.98)	<.0001

Abbreviations: ARCD, AIDS-related central nervous system disorder; CI, confidence interval; CVD, cerebrovascular disease; DSP, distal symmetric polyneuropathy; IRR, incidence rate ratio.

neurocognitive diagnoses, the grooved pegboard test had the potential to artificially inflate associations with the MHMS. We also controlled for the presence of symptomatic DSP given its role as a potential alternative source of gait abnormality. The model (Table 4) revealed that CVD (1.57 [95% CI, 1.16–2.13], $P = .003$), ARCD (1.86 [95% CI, 1.17–2.98]; $P = .009$), and symptomatic DSP (1.67 [95% CI, 1.27–2.20]; $P = .0002$) were independently associated with MHMS; HAND diagnosis was not. In recognition of the complexity of our patient population, we also repeated the multivariate model with the following variations. First, we substituted a narrower definition of CVD in which "neuroimaging findings consistent with small vessel ischemic changes" alone did not result in a classification of CVD. Second, in recognition of the fact that gait was both the most common motor abnormality and also potentially the one most influenced by nonneurologic issues, we explored 2 additional multivariate models, the first excluding the 45 participants who had gait abnormality only and the second including all participants but excluding gait subscore score from the MHMS. The same variables remained independently predictive of MHMS in these additional models.

In the subscore-specific models, CVD was associated with hyperreflexia (OR, 2.3 [95% CI, 1.3–4.0]; $P = .003$). History of ARCD was associated with increased tone (OR, 3.3 [95% CI, 1.2–9.2]; $P = .02$) and hyperreflexia (OR, 4.1 [95% CI, 1.8–9.5]; $P = .001$). Symptomatic DSP was associated with weakness (OR, 2.2 [95% CI, 1.2–3.8]; $P = .009$) and gait impairment (OR, 2.2 [95% CI, 1.2–3.8]; $P = .007$). There were no significant associations between HAND diagnosis and a presence of an abnormality in any of the subscores.

DISCUSSION

We undertook the present study to characterize and understand the clinical context of motor impairments exhibited by a large, well-characterized cohort of medically complex individuals with longstanding HIV. We found that motor dysfunction was common and that gait abnormality was the most frequently observed feature, followed by impaired coordination and strength. These 3 MHMS subscores were also among the most strongly correlated, suggesting that impairment of gait, coordination, and strength together may be phenotypic for motor dysfunction in PLWH. Among clinical factors, we found that motor dysfunction was associated with CVD and prior ARCDs. Motor dysfunction was associated with HAND in univariate but not multivariate analyses, perhaps because HAND and CVD had significant overlap and CVD was the stronger correlate of motor dysfunction. We also found that motor dysfunction in PLWH did not vary with demographic or immunologic variables, including, surprisingly, age. We suspect that the lack of association of motor dysfunction with age may be due to the fact that younger participants are only enrolled in the NNTC if they have significant burden of illness, which may mask effects of age.

Given this complex motor phenotype and comorbid neurologic disease burden, the localization of the observed motor deficits is unclear. The primary source could be the extrapyramidal system, which is a well-described target of HIV-associated neuropathology [8, 33, 34]. However, this does not account for the breadth of deficits observed, which also implicate corticospinal and cerebellar function, suggesting a diffuse or multifocal pathology and/or one affecting higher order motor planning. Interestingly, neuroimaging studies have demonstrated reduced gray matter volume in PLWH in cortical regions involved in motor control, such as the premotor cortex [9], as well as corticospinal tract abnormalities [35].

Superimposed on the effects of HIV itself, some PLWH have histories of ARCD such as cerebral toxoplasmosis or progressive multifocal leukoencephalopathy, and many have ongoing CVD. It is likely that clinically observable deficits from these other conditions layer on HIV-related neuropathology to produce the complex phenotype captured by the MHMS. Indeed, there is precedent for such layering of CNS diseases in other neurodegenerative conditions. For example, in Alzheimer disease, vascular risk factors and periventricular white matter lesions (PVWMLs) are associated with extrapyramidal abnormalities (eg, postural instability and gait difficulty) [36, 37]. In patients with vascular dementia, cortical thinning as well as PVWMLs are associated with gait impairment [38].

The clinical impact of motor dysfunction on the daily lives of PLWH is currently uncertain, although there is a literature focused more specifically on gait impairment. A recent systematic review identified 17 (mostly small) studies documenting gait and balance impairment in PLWH, similar to impairments associated with falls in geriatric populations [39]. Gait disturbance in HIV has also been studied in the context of frailty [21], which has been associated with adverse outcomes in HIV, including cognitive dysfunction [40], falls [41], fractures [42], biomarkers of age acceleration [43], immune dysregulation

[44], and increased comorbidities and mortality [45]. However, whether these negative frailty outcomes are attributable to motor dysfunction specifically is uncertain.

This study has limitations. Given that the NNTC focuses on older and more medically ill participants, these findings are likely not generalizable to younger, healthier groups of PLWH. We used the MHMS instead of the full HMS. Some of the participants in this study were also included in our earlier studies of motor dysfunction [7, 14], although the data in this study are new and the larger sample size and inclusion of multiple sites allows for a focus on phenotype and the role of ARCD, which was not present in prior work. Finally, although separate examiners typically performed the neurologic examinations, medical history, and neurocognitive testing, these assessments are not truly blinded, which could potentially inflate correlations between MHMS and HAND, CVD, or ARCD status.

In summary, our study demonstrates that motor dysfunction is very common in this cohort of medically complex PLWH and most typically manifests as a complex combination of gait disorder, loss of coordination and/or strength, and sometimes additional abnormal signs on neurologic examination including hyperreflexia and increased tone. Motor dysfunction was most strongly associated with CVD, history of ARCD, and to a lesser extent, HAND. These findings raise the question of whether motor dysfunction in HIV may be the end result of neurologic multimorbidity, akin to the systemic multimorbidity that has become an increasingly recognized feature of cART-era HIV. Future studies are needed to better understand the trajectory of HIV-associated motor dysfunction over time, its neural substrates, and its potential impact on quality of life. Such improved understanding should ultimately lead to targeted interventions to reverse neurologic multimorbidity and improve motor function in PLWH.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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