The neurologic phenotype of South African patients with HIV-associated neurocognitive impairment

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Abstract

Background

The neurologic manifestations of HIV include a spectrum of HIV-associated neurocognitive disorders, as well as a cluster of neurologic symptoms and signs. The neurologic manifestations have been modified but not eradicated by antiretroviral therapy (ART). We describe the neurologic phenotype in South African patients with predominant HIV-1 subtype C infection on ART and its association with neurocognitive impairment and efavirenz and 8-hydroxy-efavirenz concentrations.

Methods

We conducted a cross-sectional analysis of the neurologic examination findings of HIV+ patients with neurocognitive impairment and used multiple linear regression to explore associations with neurocognitive impairment, efavirenz, and 8-hydroxy-efavirenz pharmacokinetics (plasma and CSF).

Results

We included 80 participants established on ART (median 40 months) of which 72 (90%) were female. The median age was 35 (interquartile range [IQR], 32-42) and the median Global Deficit Score was 0.94 (IQR 0.63-1.36). We found associations between neurocognitive impairment and neurologic signs: gait (slow walking speed [$p = 0.03$; $R^2 = 0.06$], gait ataxia [$p < 0.01$; $R^2 = 0.21$], and abnormal gait appearance [$p < 0.01$; $R^2 = 0.18$]); coordination (upper limb bradykinesia [$p < 0.01$; $R^2 = 0.10$] and lower limb bradykinesia [$p = 0.01$; $R^2 = 0.10$]); reflexes (jaw jerk [$p = 0.04$; $R^2 = 0.05$] and palmomental response [$p = 0.03$; $R^2 = 0.06$]); ocular signs (impaired smooth pursuit [$p = 0.01$; $R^2 = 0.09$] and impaired saccades [$p < 0.01$; $R^2 = 0.15$]); and motor signs (spasticity [$p \leq 0.01$; $R^2 = 0.15$] and muscle weakness [$p = 0.01$; $R^2 = 0.08$]). No significant associations were found between plasma and CSF efavirenz or 8-hydroxy efavirenz concentrations and any neurologic sign.

Conclusion

We found that individual neurologic signs were associated with neurocognitive impairment in South African HIV+ patients with predominant HIV-1 subtype C infection on ART and could be used in clinical practice to assess severity.

Registration number

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Mild forms of HIV-associated neurocognitive disorder (HAND) remain prevalent in antiretroviral-experienced patients (up to 45%).¹ HAND is diagnosed using neuropsychological testing, with patient's performance below 1 SD from the norm in at least 2 cognitive domains; however, such detailed neuropsychological assessments are not always practical in the clinical setting.^{2,3} Clinicians therefore rely on various screening tools, functional assessments, and limited neuropsychological tests for diagnosis.² Unfortunately, screening tools, including the International HIV Dementia Scale, are limited in their ability to detect milder forms of HAND with a high false-negative rate.⁴ Currently, neurologic signs are not included in HAND definitions,³ although abnormalities in gait, coordination, frontal release signs, and ocular signs (impaired smooth pursuit and saccades) have been associated with HAND in patients with predominately HIV-1 clade B infection.^{5–13} The inclusion of primitive reflexes in the case definition of HAND has been suggested.¹² Moreover, HAND neurologic manifestations have not been described in the clade C predominant HIV infected sub-Saharan Africa.^{5–13} Clade variances demonstrate different degrees of neuronal toxicity *in vitro* (reduced neurovirulence of HIV clade C vs clade B) although supporting clinical data are lacking.^{14–17} In addition, efavirenz and its metabolite 8-hydroxy-efavirenz may be an additional contributor to neurocognitive impairment.^{18–21}

Our primary objective is to describe the neurologic phenotype in South African HIV-1 positive (subtype C) patients on antiretroviral therapy (ART) who are neurocognitively impaired. Our secondary objective is to assess the association between the neurologic phenotype with neurocognitive impairment and efavirenz and 8-hydroxy-efavirenz concentrations (plasma and CSF).

Methods

Participants

We included adults (≥ 18 and ≤ 70 years) who were screened and/or participated in a randomized controlled trial (RCT) investigating lithium as adjunctive therapy in patients with neurocognitive impairment.²² Participants were established on ART for at least 6 months before the study with suppressed viral loads (HIV PCR < 400 copies/mL). Eighty participants were included in the study.

Standard protocol approvals, registrations, and patient consents

All participants gave written informed consent. The study was approved by the Stellenbosch University Health Research Ethics Committee (0578/2017) and University of Cape Town Human Research Ethics Committee (071/2013). The RCT clinical trial identifier number is PACTR201310000635418.²² The study is compliant with the STROBE statement guidelines.

Neurologic assessment

Participants received a full neurologic examination by medical practitioners who received additional training in the

neurologic evaluation. All neurologic assessments were reviewed by the same neuropsychiatrist, except for a short period of time (4 months) during which another neuropsychiatrist reviewed the participants. Each neurologic sign and symptom was assessed according to the same standardized neurologic assessment and quantified based on a previously defined tool.^{23,24} The neurologic examination included peripheral neuropathy (visual analogue scale, vibration perception, and ankle reflexes), motor system (involuntary movement, muscle bulk, tone, and power), gait (appearance, coordination, timed gait test), limb coordination (upper and lower limb), reflexes (deep tendon reflexes and the primitive reflexes including snout, grasp, palmomental, glabellar tap, and plantar response) neck stiffness, facial strength, and ocular signs (saccades and smooth pursuit).

Gait appearance was defined as normal, wide-based or weakness of foot dorsiflexors (neuropathic or “foot slapping”), bilateral spasticity (stiff “scissoring” gait), hemiparetic gait, or unable to walk. Gait coordination was defined as normal gait, mild impairment (evident only on rapid turns or tandem), moderate impairment (clear difficulty of unassisted gait), severe impairment (walking only with assistance), or non-ambulatory. Upper and lower limb coordination was defined using rapid opposition of the first and second fingers, rapid wrist rotation, and rapid foot-tapping.

To simplify the neurologic data a binary score was assigned to indicate the absence or presence of neurologic signs to allow for statistical analysis.²³

Neuropsychiatric assessment

The Global Deficit Score (GDS), a summative neuropsychology test battery score adjusted for age, education, sex, and ethnicity was calculated for each participant.²⁵ The domains (tests used) were attention (Mental Alternation Test, Digit Span, Paced Auditory Serial Addition Test), learning and memory (the Hopkins Verbal Learning Test), motor speed (Finger Tapping Dominant Hand, Finger Tapping Non-Dominant Hand, Grooved Pegboard Test Dominant Hand, Grooved Pegboard Test Non-Dominant Hand), psychomotor speed (Trail Making Test A, Color Trails Test 1, Digit Symbol-Coding), executive function (Color Trails Test 2, Stroop Color-Word Test, Wisconsin Card-Sorting Test), visual learning and memory (Rey Complex Figure), and verbal fluency (Animals and Fruit and Vegetables). A score of 0 represents no neurocognitive impairment, whereas higher values represent greater levels of neurocognitive impairment. Symptoms of depression were also screened for using the Center for Epidemiologic Studies Depression scale.

Pharmacokinetic assessment

Forty-six participants consented to lumbar punctures. CSF microbiology studies were reported on 36 participants, whereas efavirenz and 8-hydroxy-efavirenz pharmacokinetic data were available for all 46 participants.

Pharmacokinetic sampling

Paired plasma and CSF samples for efavirenz and its metabolites were collected. Participants recorded time of efavirenz dosing the night before and were admitted the following morning for pharmacokinetic sampling. Mid-dosing lumbar punctures were performed. Whole blood was collected within 45 minutes of CSF sampling, centrifuged within 1 hour of collection, aliquoted, and stored at -80°C until analysis. CSF was aliquoted and stored at -80°C until analysis.

Efavirenz and metabolites

Drug assays were performed at 2 laboratories. The analytical laboratory in the Division of Clinical Pharmacology at the University of Cape Town quantified total efavirenz in plasma and CSF using validated liquid chromatography tandem mass spectrometry (LC/MS-MS) assays. The lower limit of quantification (LLOQ) for plasma efavirenz was 19.5 ng/mL. For CSF, the LLOQ for total efavirenz was 0.5 ng/mL. The Bioanalytical Facility, Department of Molecular and Clinical Pharmacology at the University of Liverpool quantified total CSF 8-hydroxy-efavirenz and plasma 8-hydroxy-efavirenz and plasma using validated LC/MS-MS assays.²⁶ The LLOQ for CSF 8-hydroxy-efavirenz and plasma 8-OH-EFV was 3.125 and 5.0 ng/mL, respectively. Concentrations below the limit of quantification were analyzed as missing data.

Statistical analysis

Categorical data were described using proportions and depending on the number of variables, χ^2 or Fisher exact tests were used in hypothesis testing where appropriate. Numerical data distribution was assessed for normality and data were further described using means and SDs or medians and interquartile ranges (IQRs) where appropriate. If participant data were missing for a particular variable, the participant was excluded from the variable analysis with the variable sample size being adjusted accordingly each time.

For the primary outcome, associations between GDS and the individual neurologic signs and symptoms were determined using a linear regression model. A p -value of <0.05 was considered significant. The primary outcome was further explored using multivariate linear regression modeling where variables with either poor variation or too few events were excluded from the model. A p -value of <0.05 was considered significant. Secondary outcomes explored associations between efavirenz and 8-hydroxy-efavirenz plasma and CSF concentrations, and their respective plasma:CSF ratios with neurologic signs and symptoms. Linear regression models were used with a p -value of <0.05 for statistical significance.

Data availability

The investigators will share all deidentified participant data and study-related documents such as the study protocol and statistical analysis plan for further analysis after approval from the Human Research and Ethics Committee. Data requests can be made by researchers provided that the institutional

ethical approval remains active and data analysis requests are in agreement with the participant informed consent. Contact the corresponding author for data requests.

Results

Eighty participants were included in the study. All participants were black Africans, with the majority being both isiXhosa speaking ($n = 73$; 91%) and female ($n = 72$; 90%). The median GDS was 0.94 (IQR 0.63–1.36). The baseline characteristics are presented in table 1. Many participants experienced symptoms and had signs, suggestive of peripheral neuropathy ($n = 32$, 40%). However, in linear regression analysis, both subjective ($p = 0.15$) and objective peripheral neuropathy ($p = 0.11$) indicators were not found to be associated with GDS, although in multivariate analysis the vibration perception score ($p < 0.01$) was found to be associated with GDS ($p < 0.01$) (table 2). A number of neurologic signs were associated with GDS (table 3). Associations included motor signs in the form of spasticity ($p < 0.01$; $r^2 = 0.15$) and muscle weakness ($p = 0.01$; $r^2 = 0.08$); abnormalities in gait in the form of slowed walking speed ($p = 0.03$; $r^2 = 0.06$), gait ataxia ($p < 0.01$; $r^2 = 0.21$), and abnormal gait appearance ($p < 0.01$; $r^2 = 0.18$); abnormalities in limb coordination in the form of upper limb bradykinesia ($p < 0.01$; $r^2 = 0.10$) and lower limb bradykinesia ($p = 0.01$; $r^2 = 0.10$); brisk deep tendon reflexes in the form of jaw jerk ($p = 0.04$; $r^2 = 0.05$); primitive reflexes in the form of palmomental reflex ($p = 0.03$; $r^2 = 0.06$); and finally, ocular signs including impaired smooth pursuits ($p = 0.01$; $r^2 = 0.09$) and impaired saccades ($p < 0.01$; $r^2 = 0.15$). All associations were found to be positive, except for the palmomental response, which had a negative association. When included in a multivariate linear regression model, certain neurologic signs and their association with GDS remained important (table 2). Additional variables found to be associated with GDS, not established in univariate analysis, were vibration perception score as a measure of peripheral neuropathy ($p < 0.01$), the grasp reflex ($p = 0.03$), and the female sex ($p = 0.05$). CSF parameters, which included CSF-cell count, -culture, -chemistry, -albumin, and CSF: serum albumin ratios were normal (data not shown). We previously described the pharmacokinetics of efavirenz and its metabolites in plasma and CSF.²⁷ In summary, plasma efavirenz median (IQR) was 1,960 (1,390–3,200) ng/mL, range 55–18,100 ng/mL; CSF efavirenz median (IQR) was 17.25 (10.7–19.9) ng/mL, range 1.73–119 ng/mL; plasma 8-hydroxy-efavirenz median (IQR) was 1,808 (1,325.5–2,498.7) ng/mL, range 68.8–4,887.5 ng/mL; and CSF 8-hydroxy-efavirenz median (IQR) was 4.17 (3.80–5.79) ng/mL, range 3.15–9.56 ng/mL. We found no significant associations between any of the neurologic signs and symptoms and efavirenz or 8-hydroxy-efavirenz in plasma or CSF or their respective plasma-to-CSF ratios (data not shown). We previously demonstrated elsewhere that no significant associations existed between GDS and efavirenz or 8-hydroxy-efavirenz in plasma or CSF or their respective plasma-to-CSF ratios.²⁷

Table 1 Baseline characteristics of study participants (n = 80)

Characteristics	Results
Sex	
Male, n (%)	8 (10)
Female, n (%)	72 (90)
Age (y) ^a	35 (32–42)
CD4 count+ T-cell count ^a (cells/mm ³)	498 (392–625)
Viral load	
≤50 (copies/mL), n (%)	69 (86)
51–150 (copies/mL), n (%)	4 (5)
Data not available, n (%)	7 (9)
Months on ART ^a (mo)	40 (22–68)
ART regimen	
NNRTI-based, n (%)	69 (86)
PI-Based, n (%)	10 (13)
Data not available, n (%)	1 (1)
Neurocognitive impairment	
GDS overall ^a	0.94 (0.63–1.36)
GDS < 0.75, n (%)	25 (31)
GDS 0.75–1.5, n (%)	39 (49)
GDS > 1.5, n (%)	16 (20)
Years education	
≥10, n (%)	42 (55)
<10, n (%)	34 (45)
Data not available, n (%)	4 (5)
Employment status	
Unemployed, n (%)	55 (69)
Full time employed, n (%)	10 (12)
Part time, n (%)	15 (19)
Depression score	
CES-D, ^a n (%)	8 (2–14)
Home language	
IsiXhosa, n (%)	73 (91)
Sesotho, n (%)	2 (3)
Data not available, n (%)	5 (6)

Abbreviations: ART = antiretroviral therapy; CES-D = Center for Epidemiologic Studies Depression scale; GDS = Global Deficit Score; IQR = interquartile range; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI-based = protease inhibitor-based regimen.

^a Median and IQR.

This study examined the association between neurologic signs and HIV-associated neurocognitive impairment severity in a South African population with predominant clade C HIV infection.

Discussion

This study examined the association between neurologic signs and HIV-associated neurocognitive impairment severity in a South African population with predominant clade C HIV infection. We found that certain neurologic signs are associated with more severe forms of HIV associated neurocognitive impairment especially abnormalities in gait (slowed walking speed, gait ataxia, and abnormal gait appearance), coordination (bradykinesia of the upper and lower limbs), motor signs (spasticity, decreased muscle strength, hyperreflexia), reflexes (palmomental reflex) as well as ocular signs (impaired smooth pursuit and saccades). Multivariate analysis confirmed the association of motor signs (decreased muscle strength); abnormalities in gait (slowed walking speed) and ocular signs (impaired smooth pursuit) with GDS. Neurologic symptoms and signs were not associated with plasma or CSF efavirenz or 8-hydroxy-efavirenz concentrations.

Our findings replicate that of others who associated abnormalities in gait, coordination (body bradykinesia, abnormalities in rapid alternating movement), motor signs (spasticity, decreased muscle strength, hyperreflexia), frontal release signs and ocular signs (impaired smooth pursuit) with HIV-associated neurocognitive impairment.^{5–13} We in addition found that the palmomental reflex had a negative association with the GDS which is counter intuitive. The neurologic phenotype of HIV associated neurocognitive impairment has been best described during the pre-ART era.^{5–10,12} The first description in 1986 described a wide range of deficits from mild weakness and coordination disturbances to seizures, incontinence, and quadriparesis.⁵ Subsequent studies described abnormalities in rapid alternating movement, frontal release signs, extrapyramidal signs and abnormalities in eye movements demonstrating mostly abnormal smooth pursuit.^{6–10,12} Neurocognitive impairment in the post-ART era is associated with extrapyramidal signs and soft neurologic signs described in the Heidelberg Scale.^{11,13} However, the neurologic phenotype of HIV associated neurocognitive impairment is predominantly representative of a male HIV-1 clade B infected population with data lacking in females and HIV-1 subtype C infected

Table 2 Multivariate linear regression model for association between neurologic signs and symptoms and change in GDS

Predictor variable	Regression coefficient (β)	95% CI	p Value
Peripheral Neuropathy			
Subjective rating scale	0.12	−0.17 to 0.41	0.41
Vibration perception score	0.59	0.26 to 0.93	<0.01
Decreased ankle reflex	−0.04	−0.41 to 0.33	0.83
Motor			
Muscle bulk (atrophy)	0.28	−0.92 to 1.28	0.64
Muscle strength (power)	1.51	0.05 to 2.98	0.04
Gait			
Gait coordination-timed gait (slow walking speed)	0.42	0.08 to 0.75	0.02
Gait coordination (ataxia)	−0.45	−1.48 to 0.58	0.39
Gait appearance (abnormal)	1.04	−0.12 to 2.21	0.08
Coordination			
Upper extremity (bradykinesia and ataxia)	0.23	−0.07 to 0.52	0.13
Reflexes			
Deep tendon reflexes			
Increased	−0.08	−0.26 to 0.10	0.38
Jaw jerk	0.20	−0.40 to 0.80	0.51
Primitive reflexes			
Grasp reflex	1.02	0.11 to 1.92	0.03
Palmomental reflex	−0.79	−1.25 to −0.32	<0.01
Glabella tap	0.29	−0.20 to 0.77	0.24
Ocular signs			
Impaired smooth pursuit	0.48	0.00 to 0.96	0.05
Impaired saccades	0.89	−0.52 to 2.29	0.21
Sex	0.23	0.01 to 0.84	0.05

Abbreviations: CI = Confidence interval; GDS = Global Deficit Score. Bold indicates significant findings.

individuals. Clade C is the most prevalent HIV-1 subtype of sub-Saharan Africa and is predominant (89%) in our study setting (Cape Town).²⁸ This is important as basic science studies have demonstrated that HIV clade differences may vary in their neuropathologic effects, and potentially HIV associated neurocognitive impairment presentation.¹⁴ Most important is the clade variances of the Tat gene with reduced neurovirulence of HIV-C vs HIV-B in vitro.^{14,15} However, clinical and imaging studies in South Africa found that HIV-C Tat conferred similar neurotoxicity clinically to HIV-B Tat.¹⁶ A Brazilian study also found comparable

Clade C is the most prevalent HIV-1 subtype of sub-Saharan Africa and is predominant (89%) in our study setting (Cape Town).

neurovirulence between Clade B and C-infected patients from the same local population.²⁹ Our findings contribute to growing body of clinical evidence that neuropathology is similar in both Clade C and B HIV-1 subtypes. South Africa sees a high proportion of women presenting for HIV care.³⁰ HIV-positive women have an increased susceptibility to cognitive impairment particularly in psychomotor speed, attention, and motor skills, whereas no sex differences were demonstrated in HIV-negative participants.^{31,32} These differences reflect the proposed influences of “sexual dimorphism on immune function, pathogenesis and antiretroviral pharmacokinetics,” but also differences in mental health prevalence and sociodemographic patterns between sexes.^{31,32} Our study population consisted of a predominant female population, and we found similarities in the neurologic phenotype compared with a male predominant setting despite multivariate analysis demonstrating female sex to be a predictor of GDS. However, appropriately powered studies designed to further explore sex differences are required.

Current guidelines include the addition of daily functional impairment to its criteria when differentiating between symptomatic and asymptomatic neurocognitive impairment.³ The prevalence of asymptomatic neurocognitive impairment decreased from 76% to 59% when combining self-report and performance-based approaches.³³ Self-reported activities of daily living is the most convenient method to assess daily functioning but may be influenced by self-report bias, depression, and the severity of cognitive dysfunction and can therefore increase the risk for HIV-associated neurocognitive impairment false-positive errors.^{33,34} More objective but convenient approaches are needed to measure daily functional impairment in conjunction with self-report tools. The neurologic examination could potentially be used as a tool to objectively assess certain aspects of daily function (i.e., coordination and gait) and used together with self-report to further delineate functional impairment. However, further research is needed to better define the neurologic phenotype and its relationship to functional impairment.

Efavirenz is known to initially cause neuropsychiatric symptoms such as headache, dizziness, impaired concentration, abnormal dreams, and anxiety.^{35,36} This is usually transient in nature and resolves over time. Efavirenz, along with its metabolite 8-hydroxy-efavirenz, has been shown to

Table 3 Linear regression models for association between neurologic signs and symptoms and change in GDS

Predictor variable	R-squared value	Regression coefficient (β)	95% CI	p Value
Peripheral neuropathy				
Subjective rating scale	0.03	0.24	−0.09 to 0.56	0.15
Vibration perception score	0.03	0.31	−0.08 to 0.69	0.11
Decreased ankle reflex	0.02	0.21	−0.14 to 0.56	0.23
Motor				
Muscle bulk (atrophy)	<0.01	0.63	−0.82 to 2.08	0.39
Involuntary movement	No abnormalities found			
Muscle tone				
Increased	0.15	2.50	1.15 to 3.85	<0.01
Decreased	No abnormalities found			
Muscle strength (power)	0.08	1.79	0.39 to 3.20	0.01
Gait				
Gait coordination-timed gait (slow walking speed)	0.06	0.43	0.05 to 0.80	0.03
Gait coordination (ataxia)	0.21	1.14	0.63 to 1.66	<0.01
Gait appearance (abnormal)	0.18	1.25	0.64 to 1.86	<0.01
Coordination				
Upper extremity (bradykinesia and ataxia)	0.10	0.47	0.16 to 0.79	<0.01
Lower extremity (bradykinesia and ataxia)	0.10	0.49	0.15 to 0.82	<0.01
Reflexes				
Deep tendon reflexes				
Increased	0.02	0.40	−0.26 to 1.07	0.23
Jaw jerk	0.05	0.63	0.03 to 1.23	0.04
Decreased	0.01	0.15	−0.18 to 0.48	0.36
Primitive reflexes				
Snout reflex	<0.01	−0.10	−0.54 to 0.34	0.64
Grasp reflex	0.04	0.88	−0.14 to 1.90	0.09

Table 3 Linear regression models for association between neurologic signs and symptoms and change in GDS (continued)

Predictor variable	R-squared value	Regression coefficient (β)	95% CI	p Value
Palmomental reflex	0.06	−0.47	−0.90 to -0.05	0.03
Glabellar tap	<0.01	0.19	−0.26 to 0.64	0.40
Babinski response	<0.01	−0.18	−1.64 to 1.28	0.80
Other				
Neck stiffness	No abnormalities found			
Ocular signs				
Impaired smooth pursuit	0.09	0.74	0.22 to 1.25	<0.01
Impaired saccades	0.15	2.50	1.15 to 3.85	<0.01
Facial strength	No abnormalities found			

Abbreviations: CI = Confidence interval; GDS = Global Deficit Score. Bold indicates significant findings.

be neurotoxic through a range of different mechanisms even at therapeutic concentrations.^{18,19,37} Patients starting efavirenz-based ART rather than protease inhibitors or all-nucleoside reverse transcriptase inhibitor regimens had less improvement in neurocognitive function scores after 48 weeks in a RCT.²⁰ Patients from the CNS HIV Antiretroviral Therapy Effects Research cohort who received efavirenz performed worse in several cognitive domains compared with protease inhibitor users after more than a year of ART.²¹ A recent case series report of 20 participants describes efavirenz toxicity as a reversible clinical syndrome of ataxia and encephalopathy in underweight and presumed genetic slow metabolizers on long-term ART.³⁸ Efavirenz and 8-hydroxy-efavirenz were therefore important confounding factors to consider in our population. No patients in our study had efavirenz toxicity, which may explain the lack of association between efavirenz and 8-hydroxy-efavirenz with neurologic signs.

Our study has a number of limitations. First, the primary RCT on which our study is based was not originally designed to look at associations between neurologic manifestations and the GDS.²² Second, the primary RCT included participants with moderate to severe neurocognitive impairment (GDS ≥ 0.5), and our distribution of impairment was skewed; therefore, limiting our ability to describe associations with milder forms of neurocognitive impairment. Third, our study was observational in nature and not appropriately powered to allow for accurate multivariate linear regression modeling. In addition, without matched HIV-seronegative controls, the true

predictive value of certain neurologic signs and symptoms could not be reliably established. Fourth, examining doctors were only blinded to the degree of neurocognitive impairment and not to the participant's HIV status during neurologic examination. For this reason, examination bias may have been introduced. In addition, although 1 neuropsychiatrist reviewed the majority of neurologic assessments, inter-rater variability may have been introduced when the other neuropsychiatrist took over the review process temporarily for 4 months. However, this inter-rater variability was likely minimal with the use of a standardized neurologic assessment tool. Fifth, no measure of functional ability was assessed in this population. This limited our ability to reliably assess the effect of neurologic signs on activities of daily living or to be able to define HAND stages. Last, it is possible that some of our findings are due to peripheral neuropathy rather than the CNS disease.

Neurologic signs could be used as a pragmatic and easy to determine marker of neurocognitive decline in a busy clinic setting where it could be used to augment the clinical assessment of HAND, especially when the availability of neuropsychological testing is limited. If subtle neurologic signs can be picked up early on routine neurologic examination in HIV-positive patients, the severity of neurologic signs can be monitored on subsequent visits and can provide a potential indication for further work up and/or treatment. This can take the form of monitoring anti-retroviral compliance, the need to refer for more formal HAND testing or the need to assess for functional impairment secondary to either the neurocognitive impairment or the neurologic signs itself.

In summary, we found that certain neurologic signs are associated with more severe forms of HIV-associated neurocognitive impairment, especially abnormalities in gait, coordination, motor signs, reflexes as well as ocular signs in South African patients with HIV-associated neurocognitive impairment with predominant HIV-1 subtype C on ART. Our findings do not suggest a difference in neurologic phenotype between HIV clade C and B or between male and female patients. Neurologic symptoms and signs were not associated with plasma or CSF efavirenz or 8-hydroxy-efavirenz concentrations.

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TAKE-HOME POINTS

- Neurologic signs could be used as a pragmatic and easy to determine clinical marker of neurocognitive status.
- Neurologic signs could be used to augment the clinical assessment of HIV-associated neurocognitive impairment, especially when the availability of neuropsychological testing is limited.
- The neurologic phenotype does not seem to be affected by clade or sex differences.
- The concentrations of efavirenz and its metabolites 8-hydroxy-efavirenz do not seem to alter the neurologic phenotype.

Disclosure

The authors report no disclosures relevant to the manuscript. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

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Eric H. Decloedt, MBChB, PhD	University of Stellenbosch, Cape Town, South Africa	Designed and conceptualized the study; major role in the acquisition of data; interpreted the data; and revised the manuscript for intellectual content.

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