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Neurologic manifestations of human immunodeficiency virus-2: dementia, myelopathy, and neuropathy in West Africa

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Abstract While well documented in human immunodeficiency virus (HIV)-1, neurologic sequelae have not been systematically evaluated in HIV-2. After excluding for confounding comorbidities, 67 individuals from a rural cohort in Guinea-Bissau (22 HIV-2 participants, 45 seronegative controls) were evaluated. HIV+individuals were divided into CD4<350 and CD4≥350 for analysis. HIV-associated neurocognitive disorders (HAND), assessed by the International HIV Dementia Scale (IHDS), distal sensory polyneuropathy (DSPN), and myelopathy were the main outcome variables. In univariate analysis, there was no difference in IHDS scores among groups. When analyzed by primary education attainment, IHDS scores were nonsignificantly higher (p=0.06) with more education. There was no significant difference in DSPN prevalence among groups; overall, 45% of participants had DSPN. There were no cases of myelopathy. In multivariate linear regression, higher IHDS scores were significantly correlated with older age (coefficient=−0.11, p<0.001). Logistic regression analysis showed that older age (odds ratio (OR) 95% CI 1.04–1.20), lower CD4 count (OR 95% CI 0.996–0.999), and higher BMI (OR 95% CI 1.02–1.43) significantly predicted the presence of DSPN. While a significant increase in cognitive impairment was not observed in HIV-2-infected individuals, the study suggests the IHDS may be a less effective screening tool for HAND in settings of lower educational attainment as encountered in rural Guinea-Bissau. Similar to HIV-1, DSPN seems to occur with lower CD4 counts in HIV-2. Further study of the viral–host interactions in HIV-2 and its consequent neurological diseases may provide an avenue for understanding the epidemic problems of HIV-1.

Keywords HIV · Neurology · Polyneuropathy · HIV-associated neurocognitive disorder · HAND

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Introduction

Several neurologic consequences have been recognized during human immunodeficiency virus (HIV) infection. Thus far, the neurologic sequelae of HIV-1 are better described than in HIV-2. HIV-1-related neurologic syndromes include HIV-associated neurocognitive disorders (HAND), distal sensory polyneuropathy (DSPN), and vacuolar myelopathy (VM) (Boisse et al. 2008; Letendre et al. 2009; McArthur et al. 2010). Subclinical neurologic deficits are also prevalent, including deficits in cognition in over half of treated patients and neuropathy in similar numbers (Simioni et al. 2010; Antinori et al. 2007; Ellis et al. 2010).

Characterization of HIV-2 neurological disease has been limited to case reports and studies with ill-defined criteria for neurologic diagnosis. Studies in the early 1990s from West Africa noted myelopathy, neuropathy, meningoencephalitis, and pathologically diagnosed HIV-encephalitis among HIV-2 individuals (Ramiandrisoa et al. 1991; Lucas et al. 1993). More recently, Martinez-Steele et al (2007) noted "neurological impairment sufficient to prevent inde-

pendent daily activities" in 10.3% of its HIV-2 cohort. Other case reports and studies have reported progressive multifocal leukoencephalopathy, demyelinating encephalomyelitis, toxoplasmosis, cryptococcal meningitis, and spastic paraplegia (Klemm et al. 1988; Mabey et al. 1988; Moulignier et al. 2006; Martinez-Steele et al. 2007). There is evidence of HIV-2 cerebrospinal fluid (CSF) infiltration and central nervous system (CNS) histopathology indistinguishable from HIV-1 that indicates a basis for neurologic disease in HIV-2 individuals; specifically, multinucleated giant cells in brain specimens and HIV-2 RNA in CSF have been demonstrated in HIV-2 individuals (Lucas et al. 1993; Arvidson et al. 2004).

Neurologic studies have been challenging in the developing world (Robertson et al. 2009). Much neuropsychological testing has not been validated and requires local, matched controls as a basis for normal values. There are also limited personnel who are trained in neuropsychological testing or clinical neurology. Perhaps secondary to the scarcity of neurologic expertise along with the geographic restriction of HIV-2 to West Africa, there are no studies to date which systematically evaluate HIV-2 individuals by clinical neurologic and neuropsychological examination.

Methods

Design This is a cross-sectional study of the Caio HIV-2 cohort. The cohort was established in 1989 at the Medical Research Council Laboratories (MRC) in Caio, Guinea-Bissau. Three cross-sectional serological surveys for HIV-1 and HIV-2 status have been conducted, most recently in 2006 (Tienen et al. 2010). For this study, HIV-2 seropositive individuals and controls matched for sex, age, and area of living within the community were recruited for examination by the coordinating center in Caio. Exclusion criteria included treatment with antiretroviral therapy (ARVs), HIV-1 or human T-lymphotropic virus (HTLV)-1 co-infection, serum thyroid function or vitamin B12 abnormalities, active malaria infection (48 tested by rapid malaria test, otherwise excluded by clinical suspicion), syphilis infection, stroke, and active intoxication. Because high alcohol intake was common in the population of Caio, participants not acutely impaired at the time of the exam were included in the study. HIV-1 and HIV-2 status, CD4 count, and viral load were reassessed from blood samples drawn on the day of the clinical exam; laboratory tests were also performed for the presence of HTLV, malaria, syphilis, vitamin B12 level, thyroid function, and hemoglobin level. Laboratory testing was conducted according to standard procedures at MRC facilities and an associated laboratory in Dakar, Senegal. The protocol was approved by the MRC Ethical Committee in The Gambia, the Ministry of Health of Guinea-Bissau, and the Washington University School of Medicine Institutional Review Board. Informed consent was obtained from all participants at the time of enrollment.

Clinical assessment of cohort A medical history screening for education level, comorbid conditions, and overall functional status was conducted (Table 1). A brief psychomotor and neuropsychological evaluation was conducted, as well as assignment of a Karnofsky Performance Scale score (Karnofsky et al. 1948) and Memorial Sloan Kettering dementia score (MSK; Table 1) (Price and Brew 1988). The International HIV Dementia Scale (IHDS) (Sacktor et al. 2005; Riedel et al. 2006; Njamnshi et al. 2008) was used to screen for neurocognitive impairment. The clinical neurologic exam was modified from the international AIDS

Table 1 Assessed demographic and clinical variables

Medical history and demographics	Functional status	Neuropsychological testing	Neurologic examination
Age	Work status	Timed gait	Neck stiffness
Sex	Fatigue	Finger tapping speed	Eye movement
Education level	Ambulation	(dominant hand)	Facial sensation
Diabetes	Concentration	Grooved pegboard	Facial strength
Hypertension	Memory	Animal naming	Quantitative vibration perception
Head trauma	Sleep	Short story	Pinprick sensation
Stroke	Language	IHDS	Motor tone
Hepatitis	Karnofsky score	Finger tapping speed	Motor strength
Syphilis	MSK score	(nondominant hand)	Deep tendon reflexes
Mood		Alternating hand sequence	Extensor plantar response
Seizures		Four-word recall	Limb coordination
Headache			Pronator drift
			Romberg
			Gait

Clinical Trials Group neurologic evaluation designed for A5199 (Table 1). Each exam was limited to 2 h per participant. Medical histories were collected by trained local staff on paper forms that were translated into Portuguese. Clinical examination data were collected by medically trained personnel (two neurology residents and a senior medical student), with the aid of an experienced translator; all were blinded to the HIV status of participants. The IHDS was administered by local staff after a short, intensive training. Examinations were conducted over two months in the fall of 2009 and an additional 2 weeks in the spring of 2010.

Definition of three main outcome variables HAND, DSPN, and myelopathy were the three main outcome variables. HAND was evaluated by IHDS total score and MSK stage. The impact of HIV-2 infection was estimated by comparing performance in the infected population with the HIV seronegative group. DSPN was defined based on the American Academy of Neurology recommendations for a formal case definition in field or epidemiological studies (England et al. 2005). The definition was a composite score of diminished or absent distal symmetric vibratory or pinprick sensation of the lower extremities, history of neuropathy symptoms (numbness, paresthesias, or burning pain), and diminished or absent ankle reflexes bilaterally. Presence of all three variables was defined as probable DSPN, two variables including neuropathy symptoms was defined as possible symptomatic DSPN, and two variables excluding neuropathy symptoms was defined as possible asymptomatic DSPN. Myelopathy was defined as a composite score of four variables: symptoms of bladder problems, increased tone in the lower extremities bilaterally, extensor plantar responses bilaterally, and a bilateral spastic gait. Three out of four variables was defined as probable myelopathy and two variables as possible myelopathy.

Data analysis HIV-2 participants were stratified based on absolute CD4 counts (<350 and ≥350 cells/μl) and compared to seronegative controls. One-way analysis of variance was used to compare the groups on continuous variables, if the assumptions for normality and equal variances were met. Continuous variables without normal distributions were analyzed using the Kruskal–Wallis test. Fisher's exact test was used to compare categorical variables.

Multiple linear regression was performed to assess the association of IHDS with HIV-2 status, controlling for age, sex, and alcohol consumption. Clinically significant predictor variables were entered into the model, including viral load and absolute CD4 count. A similar multiple regression analysis was performed with CD4 percentage in place of absolute CD4 count. Forced entry and forward selection models yielded similar results. Regression diagnostics methods demonstrated that the assumptions of constant variance and normality of residuals were met.

Logistic regression was used to assess the association of DSPN with HIV-2 status using the same predictor and control variables as the multiple regression analysis. Forced entry and forward selection models yielded similar results. Regression diagnostic methods demonstrated an acceptable fit of the final model. Only forward selection models with significant independent variables were reported for both multiple and logistic regression.

Excluding HIV-2 status from 1989 and 1997, overall >98% of data were present. Calculations were made with the available data. HIV-2 status from 1989 and 1997 was available for 23 and 38 patients, respectively. Besides blood pressure (eight missing values), no measure had more than three data points missing.

Data were entered in duplicate. Statistical analysis was conducted using Stata 11.0 (Stata Corp., College Station, TX).

Results

A total of 108 individuals from the cohort had known HIV-2 seropositivity from previous serosurveys (Fig. 1). After exclusions for availability and confounding comorbidities, 67 individuals remained in the final analysis, of which there

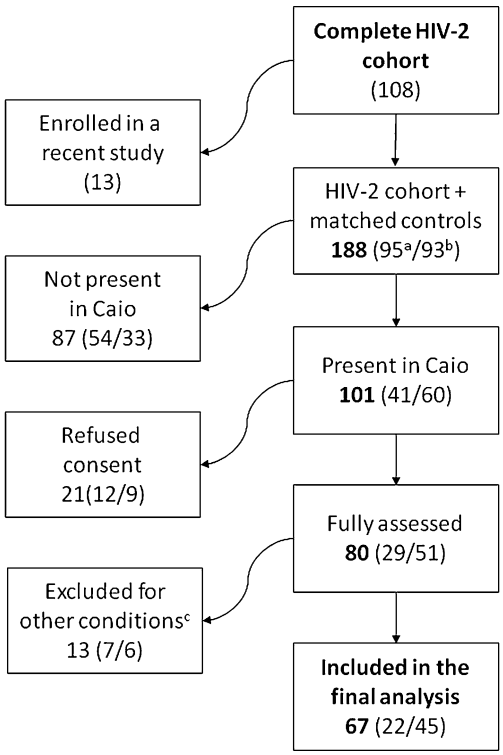

Fig. 1 *a* HIV-2, *b* control, *c* HIV-1, HTLV-1, stroke, syphilis, hypothyroidism, malaria

were 11 HIV-2 individuals with CD4<350, 11 HIV-2 individuals with CD4≥350, and 45 seronegative controls.

Individuals in the three groups were not statistically different regarding sex, age, or level of education (Table 2). Comorbidities, including self-reported diabetes mellitus, hepatitis, asthma, head trauma, and seizures, were not statistically different and were low in prevalence. Elevated blood pressure, defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg based on the single visit, was much higher than self-reported history of hypertension. Participants had similar body mass index (BMI) among the three groups (mean 22.0–22.4 kg/m^2), as well as high levels of daily alcohol consumption (mean 0.6–0.9 L in the three groups). There was a statistical difference in hemoglobin level for the three groups (p=0.03), with the lowest hemoglobin (13.1 g/dL) in the CD4<350 HIV-2 group.

Five participants were known to be HIV-2 seropositive for over 20 years and six for over 10 years. The median viral load was <100 copies/mL, the detection limit of the assay in the CD4≥350 group and 318 copies/mL in the CD4<350 group. Two individuals had known viral loads greater than 10,000 copies/mL; none had more than 100,000 copies/mL.

The univariate analyses for the main outcome variables—HAND (estimated by IHDS), DSPN, and myelopathy—were not significantly different among groups (Tables 3 and 4). IHDS total score and subscores were not statistically different among groups. When analyzed by education level, IHDS total score was nonsignificantly higher among those with at least a primary education (mean IHDS total score 8.9 vs. 7.6, p=0.06). A similar result was found when analyzed by literacy. Among the groups, 27%, 18%, and 11% of CD4 <350, CD4≥350, and control individuals, respectively, demonstrated MSK>0.5 or unequivocal impairment characteristic of HAND (Table 5). DSPN was possible or probable in 45% of the overall cohort (36–64%). The difference among groups for DSPN or its component variables was not statistically significant. There was no myelopathy in any of the groups. Among the component variables for myelopathy, extensor plantar responses, bilateral lower extremity increased tone, and spastic gaits were not observed in any of the participants.

Table 2 Medical history and demographics

Variable	HIV-2 (CD4<350; n=11)	HIV-2 (CD4≥350; n=11)	Control (n=45)	P value
Sex, no. (%)				
Male	0 (0%)	4 (36%)	11 (24%)	0.10
Female	11 (100%)	7 (64%)	34 (76%)	0.10
Mean age, years	55.1	50.3	51.9	0.68
Male	NA	46.2	45.4	0.89
Female	55.1	52.6	54	0.93
Primary education or greater, no. (%)	4 (36%)	5 (45%)	12 (27%)	0.45
Ability to read and write, no. (%)	4 (36%)	5 (45%)	9 (20%)	0.15
Employed, no. (%)	10 (91%)	11 (100%)	45 (100%)	0.33
Mean body mass index, kg/m^2	22	22.1	22.4	0.92
Mean hemoglobin, g/dL	13.1	14.3	14.3	0.03*
Mean systolic blood pressure, mm Hg	122	134	134	0.46
Mean diastolic blood pressure, mm Hg	84	92	87	0.68
Elevated blood pressure, no. (%)	2 (29%)	5 (56%)	23 (53%)	0.50
Hypertension, no. (%)	1 (9%)	4 (36%)	9 (20%)	0.32
Diabetes mellitus, no. (%)	0 (0%)	0 (0%)	1 (2%)	1.00
Hepatitis, no. (%)	1 (9%)	0 (0%)	2 (4%)	0.70
Asthma, no. (%)	0 (0%)	0 (0%)	3 (7%)	1.00
Head Trauma, no. (%)	1 (9%)	0 (0%)	1 (2%)	0.55
Seizures, no. (%)	0 (0%)	0 (0%)	0 (0%)	1.00
Mean daily alcohol consumption, L	0.5	0.9	0.8	0.53
Mean absolute CD4 count, cells/mL	182	913	910	0.0001*
Mean CD4 percentage	20.9	41.2	42.9	0.0001*
Median viral load[a] (IQR)	318 (<100–3,115)	<100 (<100 to <100)	NA	0.02*
HIV-2+ since 1989, no.	2	3	NA	NA
HIV-2+ since 1997, no.	4	2	NA	NA

[a] Viral load of <100 copies is the detection limit of the assay

*p<0.05

Table 3 Neuropsychological testing, including the IHDS

Variable	HIV-2 (CD4<350; n=11)	HIV-2 (CD4≥350; n=11)	Control (n=45)	P value
Mean IHDS total score	8	8.2	8.0	0.90
Mean IHDS fingertapping subscore	2.4	2.5	2.4	0.90
Mean IHDS hand sequence subscore	2.4	2.9	2.3	0.56
Mean IHDS 4-word recall subscore	3.3	2.9	3.3	0.72
Timed gait, mean seconds	16.8	13.6	13.8	0.57
Finger tapping test, dominant hand, mean no.	43.8	39.9	45.1	0.16
Grooved pegboard, dominant hand				
No. who completed task (%)	6 (55%)	7 (64%)	23 (51%)	0.82
Mean seconds to complete task	135.7	137.9	133.9	0.94
Grooved pegboard, nondominant hand				
No. who completed task (%)	5 (45%)	6 (55%)	19 (42%)	0.82
Mean seconds to complete task	155.4	147.7	145.6	0.91
Animal naming, mean no. correct	10.5	11.5	13	0.05
Short story, mean no. correct	5.2	5.2	5.3	0.83

Only one participant complained of bladder problems (specifically hesitation).

Other neurologic complaints and self-reported functional status, including the Karnofsky score, were not statistically different among groups (Table 6). There was a nonsignificant difference in the prevalence of concentration problems among the three groups (p=0.08). The highest proportion of complaints (36%) was in the CD4<350 HIV-2 group. There was a similar nonsignificant trend in the prevalence of language problems among the groups, with the greatest proportion of problems (27%) in the CD4<350 HIV-2 group.

Other neuropsychological testing (timed gait, finger tapping, grooved pegboard, animal naming, short story task) were not statistically different among groups. However, there was a trend toward better animal naming with decreasing disease severity (by CD4 count). Comparison of neurological exam findings showed no pattern of significant difference among groups.

Table 4 Distal sensory peripheral neuropathy (DSPN) and myelopathy

Variable	HIV-2 (CD4<350; n=11)	HIV-2 (CD4≥350; n=11)	Control (n=45)	P value
DSPN, no. (%)				
None	4 (36%)	7 (64%)	26 (58%)	0.33
Possible asymptomatic	1 (9%)	0 (0%)	0 (0%)	
Possible symptomatic	4 (36%)	3 (27%)	16 (36%)	
Probable	2 (18%)	1 (9%)	3 (7%)	
All cases (probable+possible)	7 (64%)	4 (36%)	19 (42%)	0.41
Numbness, no. (%)	7 (64%)	4 (36%)	21 (47%)	0.51
Paresthesia or burning pain, no. (%)	7 (64%)	4 (36%)	22 (49%)	0.44
Any neuropathic symptoms, no. (%)	9 (82%)	6 (55%)	34 (76%)	0.33
Decreased ankle reflexes[a], no. (%)	6 (55%)	6 (55%)	21 (48%)	0.88
Decreased distal vibration or pinprick[a], no. (%)	5 (45%)	1 (9%)	9 (20%)	0.17
Myelopathy, no. (%)				
Probable	0	0	0	1.00
Possible	0	0	0	1.00
Increased tone, lower extremities^, no.	0	0	0	1.00
Bilateral spastic gait, no.	0	0	0	1.00
Extensor plantar response^, no.	0	0	0	1.00
Bladder problems, no.	0	0	1	1.00

[a] Symmetric

Table 5 Memorial Sloan Kettering dementia score

MSK Score*	HIV-2 (CD4<350; *n*=11)	HIV-2 (CD4≥350; *n*=11)	Control (*n*=44)
0	8 (73%)	9 (82%)	29 (66%)
0.5	0 (0%)	0 (0%)	10 (23%)
1	2 (18%)	2 (18%)	4 (9%)
2	1 (9%)	0 (0%)	1 (2%)

MSK Memorial Sloan Kettering
*p=0.17

Multiple linear regression showed that age was the only significant variable in the model for predicting IHDS total score (coefficient=−0.11, coefficient 95% CI=[−0.15, −0.07], p<0.001). Specifically higher IHDS scores were associated with younger age. Age accounted for 28% of the variation in IHDS score.

The overall logistic regression model for presence of DSPN was statistically significant (logistic regression χ^2= 30.78, degrees of freedom (*df*)=3, p<0.0001 in the forward selection model). Significant predictors in the model included age (odds ratio (OR)=1.12, OR 95% CI=[1.04, 1.20]), CD4 count (OR=0.998, OR 95% CI=[0.996, 0.999]), and BMI (OR=1.21, OR 95% CI=[1.02, 1.43]).

Discussion

IHDS

HAND remains one of the most frequent neurological complications of HIV-1, but the most serious form, HIV-associated dementia, is seen primarily in very advanced or untreated patients (McArthur 2004; McArthur et al. 2005). Based on the rate of >80% LTNPs with HIV-2, a relatively low prevalence of dementia was expected in HIV-2 individuals. Exclusion of the milder forms of HAND is very difficult across cultural and language barriers, making it unclear how prevalent HIV-associated neurocognitive changes are in the developing world. Well-designed cohort studies have been one strategy for effectively detecting the impact of a disease. In the Caio cohort, we found no evidence of a difference in IHDS total score among HIV-2 and control groups. After adjusting for age, the mean effect of HIV-2 infection on IHDS total score was 0.26 (95% CI= [−0.87,1.38]); despite the limited size of this study, it provides good evidence that HIV-2 did not decrease the mean IHDS total score by more than 0.9 in infected individuals in this population. Among the groups, there was a nonsignificant trend of higher rates of MSK>0.5 with more severe HIV-2 disease. In addition to this trend being consistent with a CNS effect from HIV-2, the statistical equivalence with a high MSK>0.5 rate in controls (11%) suggests the presence of another etiology for dementia. The five individuals in the control group with MSK>0.5 were 64–79 years old, suggesting an age-related dementia not diagnosed by the screening tests in this study. In the HIV-2 groups, the age range for the four individuals with MSK=1 was younger (50–67 years) and does not fully explain the high prevalence of dementia in HIV-2 individuals. A multiple regression analysis showed that age explained 28% of the variation in IHDS total score and leaves open the possibility of HIV-2 or another etiology for impairment.

Our study may have been underpowered to detect a significant difference in IHDS among groups. Assuming an effect size equivalent to the original study validating the IHDS, 31 individuals per HIV+ and HIV− groups were needed to detect a significant difference (Sacktor et al. 2005). Our study had only 22 HIV-2 individuals. Given the observations of attenuated disease in non-neurological domains, it is also possible that HIV-2 yields a smaller effect size for IHDS, making the detection of a difference more unlikely. Further studies will be needed to clarify

Table 6 Other neurologic symptoms and signs

Variable	HIV-2 (CD4<350; *n*=11)	HIV-2 (CD4≥350; *n*=11)	Control (*n*=45)	*P* value
Full-time work status, no. (%)	3 (27%)	7 (64%)	16 (36%)	0.46
Mean Karnofsky score	85	93	86	0.13
Fatigue, no. (%)	9 (82%)	7 (64%)	25 (56%)	0.29
Sleep problems, no. (%)	6 (55%)	4 (36%)	20 (44%)	0.71
Ambulation requiring assistance, no. (%)	1 (9%)	0 (0%)	3 (7%)	1.00
Concentration problems, no. (%)	4 (36%)	1 (9%)	4 (9%)	0.08
Memory problems, no. (%)	7 (64%)	5 (45%)	20 (44%)	0.58
Language problems, no. (%)	3 (27%)	2 (18%)	3 (7%)	0.09
Depression symptoms, no. (%)	6 (55%)	3 (27%)	19 (42%)	0.43
Headaches, no. (%)	4 (36%)	4 (36%)	22 (49%)	0.62

whether equivalent IHDS scores were due to the low power of our study or to attenuated neurological disease in HIV-2.

Both controls and HIV-2 groups in this study had lower mean IHDS total scores than observed in Ugandan subjects who validated the IHDS (8.0–8.2 vs. 9.9–11) (Sacktor et al. 2005) Lower educational attainment in Guinea-Bissau is a plausible factor. Ugandans in the original IHDS study had an average of 9 years education. By comparison, 66% of the Caio cohort had no formal education, and only 19% attained some secondary education. A recent study in India with HIV-1 individuals (absolute CD4 count>400) demonstrated that lower educational attainment had a significant negative effect on IHDS total score that was greater than the effect of HIV serostatus, which was nonsignificant (Waldrop-Valverde et al 2010). When the Caio cohort was evaluated based on education level, a trend towards higher scores was seen among those with some primary education or greater (p=0.06). Our study suggests, like the Waldrop-Valverde et al. study, that the IHDS may be affected by educational attainment, making it less sensitive (or biased towards lower scores) in populations without formal schooling.

DSPN

DSPN is the most common neurologic disorder in HIV-1 (Pardo et al. 2001; Bacellar et al. 1994). Data from this study suggest that HIV-2 may demonstrate a similar pattern of DSPN as HIV-1.

Previous studies defining DSPN as two signs +/− symptoms (similar to probable DSPN in this study) had DSPN prevalence of 10–37% in non-ARV HIV-1 cohorts, similar to the 9–18% found in our HIV-2 groups (Maritz et al. 2010; Sithinamsuwan et al. 2008; Watters et al. 2004). When using a less conservative definition of DSPN (one sign +/− symptoms), the same studies showed 43–49% prevalence, comparable to the 50% prevalence in our combined HIV-2 groups. Of note, the prevalence of DSPN in our control group (7%) was not unlike reports from previous studies of the general non-HIV population. In studies with a definition equivalent to probable DSPN in this study, 4.2–15% of non-HIV samples demonstrated DSPN (Watters et al. 2004; Beghi and Monticelli 1998; Mold et al. 2004).

Logistic regression for DSPN showed that increased age, lower CD4 count, and higher BMI predicted increased odds of DSPN. The increasing likelihood of DSPN with age is consistent with both the HIV-1 and non-HIV literature (Ellis et al. 2010; Tagliati et al. 1999; Bacellar et al. 1994), including studies with multivariate or logistic regression analysis (Lichtenstein et al. 2005; Simpson et al. 2006; Morgello et al. 2004; Mold et al. 2004; Maritz et al. 2010).

The increased odds of DSPN with lower CD4 counts suggest that disease severity is a risk factor for DSPN in HIV-2. A similar finding has been widely demonstrated in HIV-1 (Tagliati et al. 1999; So et al. 1988; Lichtenstein et al. 2005; Childs et al. 1999). While some studies have failed to find this association (Simpson et al. 2006; Morgello et al. 2004; Maritz et al. 2010; Schifitto et al. 2002), two of these studies required their participants to have CD4<300 or advanced HIV (Simpson et al. 2006; Morgello et al. 2004). The inclusion criteria eliminated higher CD4 counts and thereby may have diminished the effect seen across a wider range of CD4 counts.

Increased odds of DSPN with higher BMI have been observed in a study of non-HIV adults 65 years and older (OR=1.06/U) (Mold et al. 2004). While the study controlled for diabetes, the authors proposed that undiagnosed diabetes may have contributed to the association of BMI and DSPN. In this study, diabetes was only assessed by self-report, leaving the possibility that undiagnosed diabetes fueled the association between BMI and DSPN (Novella et al. 2001). However, other studies, both with HIV-1 and non-HIV samples, have failed to find an association between BMI and DSPN (Tagliati et al. 1999; Maritz et al. 2010; Childs et al. 1999; Sithinamsuwan et al. 2008; Teunissen et al. 2002).

Alcohol consumption may have affected the prevalence of DSPN in this study given the reported consumption of 0.6–0.9 L/day. The typical alcoholic beverages consumed in Caio were cashew wine, palm wine, and beer. Although we could not show an association of DSPN to quantity of alcohol consumed, the widespread high intake may well have influenced DSPN in this community. The single predictor in multiple regression analysis for neuropathy on one study was the total lifetime dose of alcohol (Monforte et al. 1995). Other nutritional deficiencies which were not specifically evaluated in the Caio cohort may also have contributed to the high rates of DSPN.

Myelopathy and other findings

In HIV-1, VM is the most common type of myelopathy; 5–10% of individuals with AIDS are symptomatic and VM often appears alongside dementia. A risk factor for VM is a high number of systemic AIDS-defining illnesses (McArthur et al. 2005). Given that only seven individuals had CD4<200, it is not unexpected that individuals were free of clinical myelopathy in this study.

In other neuropsychological testing, there was a nonsignificant trend of increasing problems with concentration along disease severity (controls, CD4≥350, CD4<350). In HIV-1 cohort studies with neuropsychological testing, HIV-1 individuals did more poorly than their HIV seronegative counterparts on tests of attention and concentration (e.g.,

Color Trails 1 and 2, Digit Span Forward and Backwards) (Valcour et al. 2007; Sacktor et al. 2005). In the study by Valcour, HIV-1 participants without dementia still performed significantly more poorly on the Color Trails 2 test. In the Caio cohort, there was also a nonsignificant trend of worsening verbal fluency (as assessed by animal naming) as well as a greater proportion of self-reported language problems with disease severity. In HIV-1 groups, problems with verbal fluency have been observed in HIV+groups compared to controls (Valcour et al. 2007).

This study had several strengths. The Caio cohort is a well-characterized sample, with three serosurveys completed since 1989. In addition, serological studies excluded a number of confounding conditions. Since the cohort is community-based and follows a large sample of HIV-2 and seronegative individuals, this study was able to assess the frequency of neurological disease representative of a rural village in West Africa. Most importantly, the exams were done with examiners unaware of the serostatus of subjects, avoiding bias introduced by knowledge of disease exposure. This study adds to the growing contingent of studies demonstrating that neurological studies can be conducted in the developing world. We were able to administer the IHDS through trained local field workers (Njamnshi et al. 2008; Riedel et al. 2006; Sacktor et al. 2005). This was the first study to systematically investigate HIV-2 neurological disease, using a thorough clinical neurological exam, medical history, and a sample of neuropsychological tests. Additionally, the study included neurological exams by clinicians with special training in neurology, adding confidence to the observation that clinically important, novel neurological presentations were not missed in this population.

There were limitations to this study. A full battery of neuropsychological tests was not possible, in part due to the low formal education level of some individuals (e.g., the Color Trails test requires knowledge of Western numerical conventions). Our study suggests that even norms from developing world populations (Sacktor et al. 2005) are higher than participants' in this setting. Much larger studies would be required to develop sensitive norms for cognitive impairment in this setting. Due to cost implications, we were also unable to evaluate the contribution of diabetes or nutritional factors possibly influencing DSPN impairment in this study. While staff involved in evaluating participants first underwent extensive training, there was no formal study of interrater reliability. Finally, this pilot study was limited by a small sample size secondary to the frequent travel and temporary relocation of Caio cohort participants.

Having demonstrated the ability to collect neurological and neuropsychological data and train staff in the administration of basic instruments, we hope it will be possible in the future to further characterize HIV-2 neurological complications in this setting. Given the frequency of neuropathy, quantitative measures of peripheral nerve integrity, such as nerve conduction studies and skin-punch biopsies, should be performed to confirm DSPN and to characterize the type of peripheral nerve pathology seen in HIV-2. It appears that specific studies of the cognitive impact of HIV-2—which could enhance our understanding of HAND a prevalent problem even in treated HIV-1 patients—will be difficult to conduct with the challenges of neurocognitive assessments across cultures. However, if biomarkers for neurocognitive dysfunction become available, HIV-2 may yet be a fruitful neurological model of long standing HIV-1 (Rowland-Jones and Whittle 2007) and help accelerate our understanding of these important neurologic viral diseases.

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Conflict of interest The authors declare that they have no conflict of interest.

References

Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, Clifford DB, Cinque P, Epstein LG, Goodkin K, Gisslen M, Grant I, Heaton RK, Joseph J, Marder K, Marra CM, McArthur JC, Nunn M, Price RW, Pulliam L, Robertson KR, Sacktor N, Valcour V, Wojna VE (2007) Updated research nosology for HIV-associated neurocognitive disorders. Neurology 2007 (69):1789–1799

Arvidson N, Gisslen M, Albert J, Brandin E, Svennerholm B, Fuchs D, Hagberg L (2004) Cerebrospinal fluid viral load, virus isolation, and intrathecal immunoactivation in HIV type 2 infection. AIDS Res Hum Retroviruses 20:711–715

Bacellar H, Munoz A, Miller EN, Cohen BA, Besley D, Selnes OA, Becker JT, McArthur JC (1994) Temporal trends in the incidence of HIV-1-related neurologic diseases: multicenter AIDS cohort study, 1985–1992. Neurology 44:1892–1900

Beghi E, Monticelli ML (1998) Chronic symmetric symptomatic polyneuropathy in the elderly: a field screening investigation of risk factors for polyneuropathy in two Italian communities. Italian General Practitioner Study Group (IGPST). J Clin Epidemiol 51:697–702

Boisse L, Gill MJ, Power C (2008) HIV infection of the central nervous system: clinical features and neuropathogenesis. Neurol Clin 26:799–819

Childs EA, Lyles RH, Selnes OA, Chen B, Miller EN, Cohen BA, Becker JT, Mellors J, McArthur JC (1999) Plasma viral load and

CD4 lymphocytes predict HIV-associated dementia and sensory neuropathy. Neurology 52:607–613

Ellis RJ, Rosario D, Clifford DB, McArthur JC, Simpson D, Alexander T, Gelman BB, Vaida F, Collier A, Marra CM, Ances B, Atkinson JH, Dworkin RH, Morgello S, Grant I (2010) Continued high prevalence and adverse clinical impact of human immunodeficiency virus-associated sensory neuropathy in the era of combination antiretroviral therapy: the CHARTER Study. Arch Neurol 67:552–558

England JD, Gronseth GS, Franklin G, Miller RG, Asbury AK, Carter GT, Cohen JA, Fisher MA, Howard JF, Kinsella LJ, Latov N, Lewis RA, Low PA, Sumner AJ (2005) Distal symmetrical polyneuropathy: definition for clinical research. Muscle Nerve 31:113–123

Karnofsky DA, Abelman WH et al (1948) The use of nitrogen mustards in palliative treatment of carcinoma. Cancer 1:634–656

Klemm E, Schneweis KE, Horn R, Tackmann W, Schulze G, Schneider J (1988) HIV-II infection with initial neurological manifestation. J Neurol 235:304–307

Letendre SL, Ellis RJ, Everall I, Ances B, Bharti A, McCutchan JA (2009) Neurologic complications of HIV disease and their treatment. Top HIV Med 17:46–56

Lichtenstein KA, Armon C, Baron A, Moorman AC, Wood KC, Holmberg SD (2005) Modification of the incidence of drug-associated symmetrical peripheral neuropathy by host and disease factors in the HIV outpatient study cohort. Clin Infect Dis 40:148–157

Lucas SB, Hounnou A, Peacock C, Beaumel A, Djomand G, N'Gbichi JM, Yeboue K, Honde M, Diomande M, Giordano C et al (1993) The mortality and pathology of HIV infection in a west African city. AIDS 7:1569–1579

Mabey DC, Tedder RS, Hughes AS, Corrah PT, Goodison SJ, O'Connor T, Shenton FC, Lucas SB, Whittle HC, Greenwood BM (1988) Human retroviral infections in The Gambia: prevalence and clinical features. Br Med J Clin Res Ed 296:83–86

Maritz J, Benatar M, Dave JA, Harrison TB, Badri M, Levitt NS, Heckmann JM (2010) HIV neuropathy in South Africans: frequency, characteristics, and risk factors. Muscle Nerve 41:599–606

Martinez-Steele E, Awasana AA, Corrah T, Sabally S, van der Sande M, Jaye A, Togun T, Sarge-Njie R, McConkey SJ, Whittle H, Schim van der Loeff MF (2007) Is HIV-2- induced AIDS different from HIV-1-associated AIDS? Data from a West African clinic. AIDS 21:317–324

McArthur JC (2004) HIV dementia: an evolving disease. J Neuroimmunol 157:3–10

McArthur JC, Brew BJ, Nath A (2005) Neurological complications of HIV infection. Lancet Neurol 4:543–555

McArthur JC, Steiner J, Sacktor N, Nath A (2010) Human immunodeficiency virus-associated neurocognitive disorders: mind the gap. Ann Neurol 67:699–714

Mold JW, Vesely SK, Keyl BA, Schenk JB, Roberts M (2004) The prevalence, predictors, and consequences of peripheral sensory neuropathy in older patients. J Am Board Fam Pract 17:309–318

Monforte R, Estruch R, Valls-Sole J, Nicolas J, Villalta J, Urbano-Marquez A (1995) Autonomic and peripheral neuropathies in patients with chronic alcoholism. A dose-related toxic effect of alcohol. Arch Neurol 52:45–51

Morgello S, Estanislao L, Simpson D, Geraci A, DiRocco A, Gerits P, Ryan E, Yakoushina T, Khan S, Mahboob R, Naseer M, Dorfman D, Sharp V (2004) HIV-associated distal sensory polyneuropathy in the era of highly active antiretroviral therapy: the Manhattan HIV Brain Bank. Arch Neurol 61:546–551

Moulignier A, Lascoux C, Bourgarit A (2006) HIV type 2 demyelinating encephalomyelitis. Clin Infect Dis 42:e89–e91

Njamnshi AK, Djientcheu Vde P, Fonsah JY, Yepnjio FN, Njamnshi DM, Muna WE (2008) The International HIV Dementia Scale is a useful screening tool for HIV-associated dementia/cognitive impairment in HIV-infected adults in Yaounde-Cameroon. J Acquir Immune Defic Syndr 49:393–397

Novella SP, Inzucchi SE, Goldstein JM (2001) The frequency of undiagnosed diabetes and impaired glucose tolerance in patients with idiopathic sensory neuropathy. Muscle Nerve 24:1229–1231

Pardo CA, McArthur JC, Griffin JW (2001) HIV neuropathy: insights in the pathology of HIV peripheral nerve disease. J Peripher Nerv Syst 6:21–27

Price RW, Brew BJ (1988) The AIDS dementia complex. J Infect Dis 158:1079–1083

Ramiandrisoa H, Dumas M et al (1991) Human retroviruses HTLV-1, HIV-1, HIV-2 and neurological diseases in West Africa. J Trop Geogr Neurol 1:39–44

Riedel D, Ghate M, Nene M, Paranjape R, Mehendale S, Bollinger R, Sacktor N, McArthur J, Nath A (2006) Screening for human immunodeficiency virus (HIV) dementia in an HIV clade C-infected population in India. J Neurovirol 12:34–38

Robertson K, Liner J, Heaton R (2009) Neuropsychological assessment of HIV-infected populations in international settings. Neuropsychol Rev 19:232–249

Rowland-Jones SL, Whittle HC (2007) Out of Africa: what can we learn from HIV-2 about protective immunity to HIV-1? Nat Immunol 8:329–331

Sacktor NC, Wong M, Nakasujja N, Skolasky RL, Selnes OA, Musisi S, Robertson K, McArthur JC, Ronald A, Katabira E (2005) The International HIV Dementia Scale: a new rapid screening test for HIV dementia. AIDS 19:1367–1374

Schifitto G, McDermott MP, McArthur JC, Marder K, Sacktor N, Epstein L, Kieburtz K (2002) Incidence of and risk factors for HIV-associated distal sensory polyneuropathy. Neurology 58:1764–1768

Simioni S, Cavassini M, Annoni JM, Rimbault Abraham A, Bourquin I, Schiffer V, Calmy A, Chave JP, Giacobini E, Hirschel B, Du Pasquier RA (2010) Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. AIDS 24:1243–1250

Simpson DM, Kitch D, Evans SR, McArthur JC, Asmuth DM, Cohen B, Goodkin K, Gerschenson M, So Y, Marra CM, Diaz-Arrastia R, Shriver S, Millar L, Clifford DB (2006) HIV neuropathy natural history cohort study: assessment measures and risk factors. Neurology 66:1679–1687

Sithinamsuwan P, Punthanamongkol S, Valcour V, Onsanit S, Nidhinandana S, Thitivichianlert S, Shikuma C (2008) Frequency and characteristics of HIV-associated sensory neuropathy among HIV patients in Bangkok, Thailand. J Acquir Immune Defic Syndr 49:456–458

So YT, Holtzman DM, Abrams DI, Olney RK (1988) Peripheral neuropathy associated with acquired immunodeficiency syndrome. Prevalence and clinical features from a population-based survey. Arch Neurol 45:945–948

Tagliati M, Grinnell J, Godbold J, Simpson DM (1999) Peripheral nerve function in HIV infection: clinical, electrophysiologic, and laboratory findings. Arch Neurol 56:84–89

Teunissen LL, Franssen H, Wokke JH, van der Graaf Y, Linssen WH, Banga JD, Laman DM, Notermans NC (2002) Is cardiovascular disease a risk factor in the development of axonal polyneuropathy? J Neurol Neurosurg Psychiatry 72:590–595

Tienen C, van der Loeff MS, Zaman SM, Vincent T, Sarge-Njie R, Peterson I, Leligdowicz A, Jaye A, Rowland-Jones S, Aaby P, Whittle H (2010) Two distinct epidemics: the rise of HIV-1 and decline of HIV-2 infection between 1990 and 2007 in rural Guinea-Bissau. J Acquir Immune Defic Syndr 53:640–647

Valcour VG, Sithinamsuwan P, Nidhinandana S, Thitivichianlert S, Ratto-Kim S, Apateerapong W, Shiramizu BT, Desouza MS,

Chitpatima ST, Watt G, Chuenchitra T, Robertson KR, Paul RH, McArthur JC, Kim JH, Shikuma CM (2007) Neuropsychological abnormalities in patients with dementia in CRF 01_AE HIV-1 infection. Neurology 68:525–527

Waldrop-Valverde D, Nehra R, Sharma S, Malik A, Jones D, Kumar AM, Ownby RL, Wanchu A, Weiss S, Prabhakar S, Kumar M (2010) Education effects on the International HIV Dementia Scale. J Neurovirol 16:264–267

Watters MR, Poff PW, Shiramizu BT, Holck PS, Fast KM, Shikuma CM, Valcour VG (2004) Symptomatic distal sensory polyneuropathy in HIV after age 50. Neurology 62:1378–1383