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Factors associated with distal symmetric polyneuropathies in adult Zambians: A cross-sectional, observational study of the role of HIV, non-antiretroviral medication exposures, and nutrition

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ABSTRACT

Background: Non-antiretroviral (ART) drug exposures and poor nutrition may be important modifiable risk factors for distal symmetric polyneuropathies (DSP) in sub-Saharan Africa.
Methods: We conducted a cross-sectional study of DSP prevalence and factors associated with DSP among clinic attendees in urban and rural Zambia. All participants underwent neurologist-performed examination. Laboratory investigations seeking comorbid risk factors for DSP were performed for DSP cases.
Results: We identified 31/137 (22.6%) HIV+ and 21/177 (11.9%) HIV− DSP cases. DSP prevalence did not differ by urbanicity, although rural participants were significantly more likely to have one asymptomatic DSP sign. Low dietary diversity, history of syphilis, history of tuberculosis, and prior metronidazole and ciprofloxacin use were associated with DSP amongst HIV+ cases, while age and education were associated with DSP in HIV− participants (all p-values $< 0{\cdot}05$). In a multivariate logistic regression model, HIV ($p = 0{\cdot}0001$) and age ($p < 0{\cdot}0001$), and ciprofloxacin exposure ($p = 0{\cdot}01$) remained independently associated with DSP. While diabetes was rare, supoptimal micronutrients levels were common among DSP cases regardless of HIV status.
Conclusions: While HIV infection is strongly associated with DSP in Zambia, history of non-ART drug exposures and low dietary diversity are also important determinants of DSP in HIV+ individuals. Treatable micronutrient deficiencies were common.

1. Introduction

Research to date on distal symmetric polyneuropathies (DSP) in sub-Saharan Africa (SSA) has focused primarily on HIV−associated DSP or toxic antiretroviral (ART) neuropathies, but the background prevalence and characteristics of DSP outside of this context is unknown. Nutritional deficiencies and other toxic exposures including treatments for common endemic infectious diseases may also be important risk factors for DSP in SSA, particularly among HIV+ individuals. Prior DSP studies have only rarely evaluated nutritional factors and often exclude persons with pre-existing risk factors other than HIV. As a consequence, there is limited understanding of the neuroepidemiological features of DSP in the region. Several studies in HIV+ populations have reported associations between DSP and food insecurity and poverty, suggesting that nutrition or environmental exposures might be important and potentially modifiable DSP risk factors [1–3]. Rural populations relying on subsistence agriculture may be especially susceptible to seasonal diet variations and food shortages compared to urban populations, but research in SSA is conducted almost exclusively in urban settings. We sought to characterize the role of urbanicity, nutritional characteristics, and non-ART neurotoxic medication exposures on the presence of DSP in Zambia, and we enriched our study with HIV+ participants to

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facilitate evaluation of the impact of HIV as well.

2. Methods

2.1. Study design and population

We conducted an observational, cross-sectional study of voluntary counseling and testing (VCT) and ART clinic attendees at two health centres in Zambia. Kamwala Health Centre is a government health centre located in the capital city, Lusaka, and serves a population of approximately 117,000 residents. Chikankata Hospital is a faith-based hospital and outpatient centre located 31 km off the main tarmac road about 125 km south of Lusaka. Chikankata serves approximately 50,000 persons, most of whom are subsistence farmers. Clinic staff were encouraged daily to refer all VCT clinic attendees with documentation of HIV serostatus and all HIV+ treatment-naïve ART clinic attendees for study eligibility assessment by research staff. However, due to low rates of identification of ART-naïve participants at the rural site during the study period, this criterion was expanded to include ART-treated HIV+ individuals without a history of dideoxynucleoside reverse transcriptase inhibitor exposure. All study participants were aged 18 or older. Exclusion criteria included inability to provide informed consent, severe leg edema or amputation, and pregnancy. Enrollment occurred from 22 April 2014 through 21 August 2014. All participants provided written informed consent. The University of Zambia Biomedical Research Ethics Committee and Michigan State University Biomedical Institutional Review Board approved the study.

2.2. Procedures

Participants were interviewed by local research personnel in the participants' preferred language between Bemba, English, Nyanja, or Tonga. Research personnel from both sites trained together at a one-day session to limit inter-site variability in interview assessments. A structured questionnaire (Appendix A) was delivered orally and captured sociodemographic and other characteristics including frequency of alcohol consumption. Food security was ascertained utilizing a survey previously employed in rural Zambia regarding: 1) taking fewer daily meals in the dry season; 2) going all day without eating in the past week, and 3) skipping one or more meals in the last week due to lack of food [1].If participants answered in the affirmative to two or more questions, they were classified as belonging to a food insecure household. Dietary diversity was assessed via the proportion of average household daily dietary energy intake in kilocalories (kcal) from maize flour, a staple food accounting for approximately two thirds of total dietary energy needs among Zambians [4]. Adult equivalent units (AEU) were calculated as one AEU for each adult and 0·7 AEU for each child in the participant's household. We classified a household as having low dietary diversity if maize flour consumption in the household exceeded 70% of total daily energy requirements (2100 kcal) per AEU per day [5]. Anthropometric measurements were also recorded. A chart abstraction tool was used to collect past medical history and prescribing information including details of specific neurotoxic drug exposures (Appendix B). However, few participants presented with medical files and participant recall was then relied upon instead. The proportion of participants with available medical files did not differ between participants with DSP (n = 12; 23.1%) and those without DSP (n = 40; 15.4%) ($p < 0.312$). For HIV+ participants, we documented time since HIV diagnosis and ART initiation, CD4 cell count within 6 months from the date of study enrollment, and hepatitis B antigen results. Hepatitis C testing was not available, but prevalence has been reported at < 1.2% among HIV+ Zambians [6].

2.3. Primary outcomes

2.3.1. DSP diagnosis and clinical case definitions

Due to lack of data regarding DSP phenotypes in SSA, we utilized a comprehensive definition for DSP diagnosis incorporating a combination of neuropathic symptoms, physical exam signs, and NCS findings defined by the American Academy of Neurology Clinical Case Definition (AAN CCD) for DSP [7]. Table 2 (found under results) provides a list of allowed DSP case definitions as well as the frequency (%) of the case definitions observed by urbanicity. We also report the prevalence of having one abnormal bilateral distal neurologic exam sign (mild vibratory loss or decreased/absent Achilles reflexes relative to patellar reflexes) in the absence of symptoms, termed one asymptomatic DSP sign, to allow comparisons to prior HIV neuropathy studies.

All study participants were examined by one of two study neurologists. For a two-week period, both neurologists were present at the rural site to reduce inter-site variability in exam procedures. Symptom assessments included the Single Question Neuropathy Screen (SQNS) and the Brief Peripheral Neuropathy Screen (BPNS) [8,9]. DSP signs were assessed using a structured exam (Appendix C) and the Utah Early Peripheral Neuropathy Screen (UEPNS) [10]. Although the UEPNS is infrequently used in HIV populations, we anticipated our population to have heterogeneous DSP etiologies not limited to HIV. Participants were considered to have probable DSP by the study neurologist if: 1) bilateral distal neuropathic symptoms of pain, parathesias, or numbness suggestive of DSP were present with or without one or more exam signs; or 2) neuropathic symptoms were absent but two or more abnormal distal bilateral neurologic exam signs were present. All participants with probable DSP were referred for nerve conduction studies to provide objective evidence for DSP diagnosis and evaluate for potential mimics.

2.4. Secondary outcomes

2.4.1. Electrophysiological and laboratory assessments

NCS were performed using the simplified protocol outlined by the AAN CCD [7]. Challenges in obtaining NCS were disproportionately encountered at the rural site due to frequent electrical outages and interferences as a result of electrical grid maintenance during study recruitment, but ultimately this only limited diagnosis in two probable DSP cases, both of which were subsequently excluded from analysis of factors associated with DSP. NCS procedures and detailed results are available as supplementary material (Appendix D). Probable DSP cases were also asked to provide a blood sample for complete blood count, blood urea nitrogen, creatinine, alanine and aspartate transaminases, thyroid stimulating hormone, free thyroxine, serum and erythrocyte folate, glycated hemoglobin (HbA1c), serum vitamin B12, and Rapid Plasmin Reagin (RPR). HbA1c was categorized as normal (< 5.7%), impaired glucose tolerance (5.7–6.4%), or diabetes (≥6.5%). Serum vitamin B12 levels were defined as low if < 200 pg/mL and borderline low if 200–300 pg/mL [11]. Low folate and borderline low folate were defined as < 3 ng/mL and 3–5.9 ng/mL, respectively. Erythrocyte folate level was considered low if < 100 ng/mL [12].

3. Statistical analysis

Extrapolating from prior studies of neuropathy prevalence in SSA, a minimum sample size of 125 HIV+ and 125 HIV− participants was anticipated to provide 98% power to detect a prevalence difference of 20% between groups, using a chi-square test with 5% significance level. Frequencies of clinical, electrodiagnostic, and laboratory findings are reported for DSP cases. All statistical analyses were carried out using SPSS version 22.0. Demographic, medical and nutritional characteristics stratified by urbanicity and HIV status and were compared using two-tailed Chi-square test for categorical variables, Student's *t*-tests for comparison of means, or a nonparametric equivalent. A two-tailed *p*-

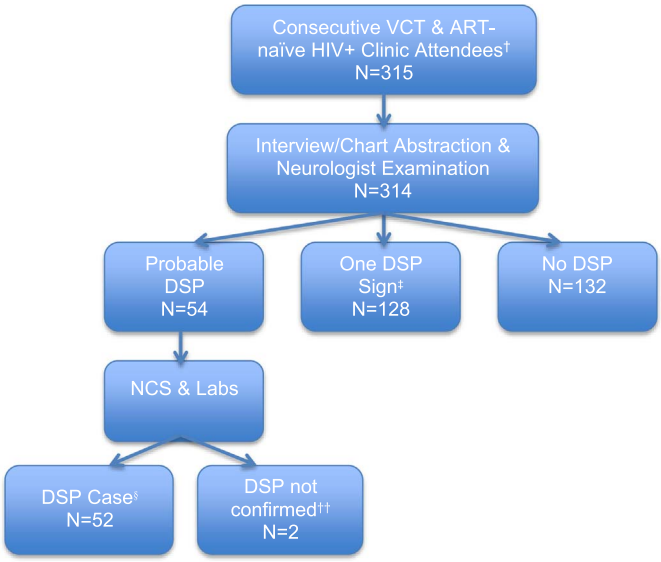

Fig. 1. Study flow chart.
†ART-treated allowed at rural site due to low rates ART-naïve clinic attendees; ‡One DSP Sign = decreased vibratory sensation or decreased/absent Achilles reflexes present bilaterally in the absence of symptoms; §Meets AAN Case Definition for DSP; ††Participants with two DSP signs but no neuropathic symptoms and did not meet the AAN CCD. These patients were excluded from further analysis of factors associated with DSP; Abbreviations: VCT = Voluntary Testing & Counselling; ART = Antiretroviral; DSP = Distal Symmetric Polyneuropathy; NCS = Nerve Conduction Studies.

value of < 0.05 was considered significant. Variables that were significant in the bivariate analysis were included in a multiple logistic regression model with DSP presence as the dependent variable. DSP severity was assessed by UEPNS score and compared with demographic, nutritional, and medical characteristics using Mann Whitney *U* tests.

4. Results

4.1. Recruitment

A schematic diagram of study recruitment and procedures is provided in Fig. 1. We identified 315 eligible participants during the study period; 314 (99.7%) consented to participate. Of the 314 participants, 177 were HIV− and 137 were HIV+. Among the HIV+ participants, 95 (69.3%) were ART-naïve, presenting within two weeks of HIV diagnosis; 42 (30.7%) were ART-treated with a median duration since HIV diagnosis of 27.5 months (IQR, 11.3–51.3). Thirty-nine (92.9%) ART-treated participants were being treated with combination tenofovir, emtracitibine, and efavirenz at the time of study enrollment.

4.2. Participant characteristics

Significant differences in baseline characteristics were observed by both HIV status and urbanicity (Table 1). Differences are consistent with prior demographic characterizations in Zambia, with the exception of BMI which was significantly lower among urban participants regardless of HIV status [13]. Nutritional characteristics also differed between sites. Rural participants were more likely to report seasonal variations in the number of meals taken daily, whereas urban participants were more likely to report going all day without eating in the past week due to lack of food. Food insecurity was more common among HIV+ rural participants than HIV+ urban participants, whereas the opposite was the case among HIV− participants. Daily alcohol intake was more common among urban HIV− participants, and urban participants were more likely to report weekly alcohol intake than rural participants. Prior metronidazole use was more common among urban participants.

4.3. DSP prevalence and clinical characteristics

The AAN CCD categories and frequencies stratified by site are provided in Table 2. Overall fifty-two (16.6%) participants met the study definition of DSP, including 31 (22.6%) HIV+ participants and 21 (11.9%) HIV− participants. DSP prevalence was similar among ART-treated (n = 10; 23.8%) and ART-naïve (n = 21, 22.3%) HIV+ participants ($p = .850$). The frequencies of neuropathic symptoms and examination abnormalities among HIV+ and HIV negative DSP cases are presented in Fig. 2. Median UEPNS score was 8 (range 1–32, IQR 5). The median BPNS pain severity score was 4 (range 1–10, IQR 5). No differences were identified between HIV+ and HIV− cases in regards to median UEPNS, or frequency or severity of BPNS symptoms.

The presence of one asymptomatic DSP sign was extremely common, with decreased vibratory sensation or decreased/absent Achilles reflexes present in an additional 53.3% (n = 56) of HIV+ and 46.5% (n = 72) of HIV− participants ($p = 0.312$). Segmental pinprick assessment was abnormal in an additional 11 (3.2%) participants. However pinprick findings were either asymmetric, not length-dependent in nature, or associated with other asymmetric exam signs suggestive of another non-DSP etiology, and therefore are not included among participants with one asymptomatic DSP sign.

Rural residence was a strong predictor of having an asymptomatic DSP sign regardless of HIV status ($p < 0.0001$). This finding remained significant in a post-hoc logistic regression analysis controlling for baseline differences in age, education, height, and HIV status with an odds ratio of 5.5 (95% CI 2.9–10.5) among rural participants.

4.4. Factors Associated with DSP

Relationships between participant characteristics and DSP are provided in Table 3. HIV status was a strong effect modifier for all variables associated with DSP. In the bivariate analysis of HIV+ participants, belonging to a household with low dietary diversity, history of tuberculosis, history of syphilis, prior metronidazole use, and prior ciprofloxacin use were all significantly associated with DSP. Among HIV− participants, only older age and lower educational levels were significantly associated with DSP. DSP prevalence did not differ by urbanicity. A multiple logistic regression analysis of DSP included HIV status, age, education level, dietary diversity, history of tuberculosis, history of syphilis, prior metronidazole use, and prior ciprofloxacin use. Because of baseline differences in participants by site, urbanicity was also included, but it did not contribute to the model. No interactions between HIV and history of tuberculosis, syphilis, metronidazole or ciprofloxacin exposures were present. Table 4 summarizes the bivariate and full model odds ratios. HIV infection, older age and history of ciprofloxacin use remained strongly associated with DSP presence in the full model. No significant associations between demographic characteristics and median UEPNS scores were found.

4.5. Electrophysiological and laboratory findings among DSP cases

Detailed electrophysiological findings are available as supplementary material (Appendix D and Fig. A.1). Complete NCS studies were available for only 20 DSP cases, of which 19 (95%) were urban study participants. Electrical grid maintenance with frequent electrical outages/interference during study recruitment resulted in disproportionately low rates of NCS completion at the rural site. Incomplete NCS data were available for 23 (74.2%) probable DSP cases while seven (22.6%) had no available NCS data at the rural site. Incomplete studies were not utilized for DSP diagnosis. Lack of data and incomplete studies might have resulted in under-diagnosis of DSP cases at the rural site, but ultimately had little impact as the predominant DSP phenotype seen had neuropathic symptoms and ≥ 2 DSP signs and did not require NCS for DSP diagnosis, as seen in Table 2. Among the 20 (38.5%) DSP cases completing NCS, 16 (80.0%) showed

Table 1
Demographic, nutrition and medical characteristics of participants by hiv serostatus and urbanicity.[†]

	HIV Status by urbanicity						HIV Status without urbanicity		
	HIV +			HIV-					
Demographic	Urban	Rural	*p*-Value	Urban	Rural	*p*-Value	HIV +	HIV-	*p*-Value
Age, mean years	33.1, n = 77 (9.9; 19–64)	38.8, n = 60 (9.4; 21–70)	0.001	29.8, n = 75 (10.6; 18–63)	39.6, n = 102 (15.8; 18–84)	< 0.001	35.6, n = 137 (10·1; 19–70)	35.4, n = 177 (14.6; 18–84)	0.915
Female gender	43/77 (55.8)	42/60 (70.0)	0.090	44, n = 75 (58.7)	51/102 (50.0)	0.253	85/137 (62.0)	95/177 (53.7)	0.137
Education, mean years	8.4, n = 70 (2.9; 0-16)	5.4, n = 60 (3.1; 0–10)	< 0.001	9.4, n = 71 (2.5; 3–16)	7.3, n = 102 (3.8; 0–14)	< 0.001	7.0, n = 130 (3.3; 0–16)	8.2, n = 173 (3.5; 0–16)	0.003
Nutrition & food security									
Height, cms	163.6, n = 77 (10.0; 140–-187)	159.6, n = 60 (9.7; 141–186)	0.021	161.6, n = 73 (8.9; 140–188)	162.9, n = 99 (9.9; 143–186)	0.380	161.9, n = 137 (10.0; 140–187)	162.3, n = 172 (9.5; 140–188)	0.733
Body-mass index, kg/m^2	21.3, n = 77 (3.6; 12.9–32.5)	25.7, n = 60 (1.1; 22.5–26.9)	< 0.001	21.9, n = 73 (3.8; 11.1–38.1)	23.9, n = 102 (1.0; 22·3–26.2)	< 0.001	23.2, n = 137 (3.5; 12.9–32.5)	23.1, n = 175 (2.8; 11.1–38·1)	0.779
Takes one or less protein meals daily	36/77 (46.8)	36/59 (61.0)	0.099	23/74 (31.1)	46/102 (45.1)	0.060	72/136 (52.9)	69/176 (39.2)	0.016
Skipped meal due to lack of food[**]	39/77 (50.6)	36/60 (60.0)	0.275	38/75 (50.7)	47/101 (46.5)	0.587	75/137 (54.7)	85/176 (48.3)	0.257
Went all day without eating[**]	29/76 (38.2)	13/60 (21.7)	0.039	37/75 (49.3)	11/102 (10.8)	< 0.001	42/136 (30.9)	48/177 (27.1)	0.466
Takes less meals during dry season	5/77 (6.5)	32/60 (53.3)	< 0.001[*]	1/75 (1.3)	37/102 (36.3)	< 0.001[*]	37/137 (27.0)	38/177 (21.5)	0.313
Low dietary diversity	18/77 (23.4)	21/60 (35.0)	0.135	16/75 (21.3)	30/102 (29.4)	0.226	39/137 (28.5)	46/177 (26.0)	0.624
Food Insecure	27/77 (35.1)	33/60 (55.0)	0·020	34/75 (45.3)	20/101 (19.8)	< 0.001	60/137 (43.8)	54/176 (30.7)	0.017
Takes alcohol daily	4/77 (5.2)	0/60 (0.0)	0.131[*]	10/75 (13.3)	2/102 (2.0)	0.005[*]	4/137 (2.9%)	12/177 (6.8%)	0.123
Takes alcohol weekly	23/76 (30.3)	4/60 (6.7)	0.001	17/75 (22.7%)	9/102 (8.8%)	0.012	27/136 (19.9%)	26/177 (14.7%)	0.239
Medical									
≥1 DSP sign[‡]	39/77 (50.6)	47/60 (78.3)	0.001	21/75 (28.0)	70/102 (68.6)	< 0.001	86/137 (62.8)	91/177 (51.4)	0.044
HIV + ART-naïve	76/77 (98.7)	19/60 (31.7)	< 0.001	–	–	–	95/137 (69.3)	–	–
ART-naïve, mean CD4 cells/μL	309.0, n = 61 (208.1; 12–866)	338.6, n = 9 (153.8; 65–547)	0.683	–	–	–	312.8, n = 70 (201.2; 12–866)	–	–
ART-treated, mean CD4 cells/μL	761.0, n = 1 (0, –)	404.3, n = 18 (278.8; 34-1061)	0.230	–	–	–	423.1, n = 19 (283.0; 34–1061)	–	–

Data are n/N (%), mean, n (SD; range).
χ^2 for categorical variables and Student's *t*-test for continuous variables unless otherwise indicated.
[†] n = 314.
[*] Fisher's Exact Test.
[**] refers to last 7 days.
[‡] DSP sign includes either reduced or absent Achilles reflex relative to patellar reflex bilaterally and/or diminished/absent vibratory sensation ($\leq$10 s) bilaterally as assessed by extinction of vibratory sensation over the great toe distal interphalangeal joint.

Table 2
Frequency of 52 DSP Cases by AAN CCD categories and urbanicity.[a]

		AAN CCD required signs & NCS				DSP cases by AAN CCD		
		Decreased or absent ankle reflexes	Decreased distal sensation	Distal muscle weakness	NCS	Urban (n = 21)	Rural (n = 31)	Total (n = 52)
AAN CCD symptoms	SDSP	Present	Present	Present[b]	NR[b]	5 (23.8%)	3 (9.7%)	8 (15.4%)
		Present	Present	Absent	NR[b]	9 (42.9%)	23 (74.2%)	32 (61.5%)
		Present	Absent	Absent	R, AB	0 (0%)	0 (0%)	0 (0%)
		Absent	Present	Absent	R, AB	2 (9.5%)	1 (3.2%)	3 (5.8%)
		Absent	Absent	Absent	R, AB	0 (0%)	0 (0%)	0 (0%)
		Absent	Present	Absent	R, NL	1 (4.8%)[d]	4 (12.9%)[c,d]	5 (9.6%)[d]
	ADSP	Present	Present	Present	R, AB	4 (19.0%)	0 (0%)[c]	4 (7.8%)
		Present	Absent	Present	R, AB	0 (0%)	0 (0%)	0 (0%)

Abbreviations: NCS = nerve conduction studies, SDSP = symptomatic DSP, ADSP = asymptomatic DSP, NR = not required; R, AB = required and abnormal; R, NL = required and normal.
[a] AAN CCD criteria adapted from: England JD, Gronseth GS, Franklin G, et al. Distal symmetric polyneuropathy: a definition for clinical research: report of the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology 2005;64:199–207.
[b] Definition does not require NCS, but all DSP cases were requested to undergo NCS.
[c] Clinical phenotype would qualify with or without abnormal NCS but were presumed normal due to incomplete NCS data.
[d] Pure small fiber phenotype.
[e] Two ADSP cases had incomplete NCS and were excluded from further analysis.

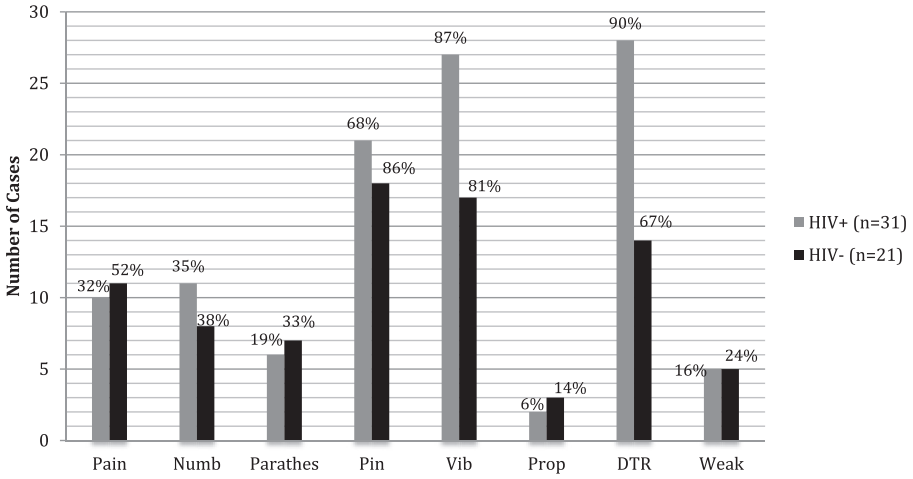

Fig. 2. Frequency of Symptoms and Signs among 52 DSP cases by HIV status.
All *p*-values < 0·05; Symptoms: Numb = numbness; Parathes = parathesias; Signs: Pin = pinprick sensation; Vib = vibration sensation; Prop = proprioception; DTR = deep tendon reflexes; Weak = extensor hallucis weakness.

electrophysiologic abnormalities consistent with a predominately sensory or sensorimotor polyneuropathy, while 4 (20%) participants had normal or borderline normal NCS findings for age. The pattern of abnormalities did not differ by HIV status.

Laboratory investigations were undertaken among 43 (82.7%) DSP cases. Missing values were due to insufficient sample collected (1.9%), declining blood draw (7.7%), and several cases in which the reason was undocumented (7.7%). Descriptive laboratory findings and comparisons by HIV serostatus are presented as supplementary material (Table A.1). Overall, no significant differences existed in laboratory findings between DSP cases with and without HIV. Erythrocyte folate was low in 28.0% (n = 7) of HIV+ and 12.5% (n = 2) of HIV− DSP cases. Vitamin B12 was low in 20% (n = 5) HIV+ and 22.2% (n = 4) of HIV− DSP cases, and an additional 12% (n = 3) of HIV+ and 33.3%

Table 3
Characteristics of participants with and without DSP by HIV status.[†]

	HIV+			HIV-			Overall		
	DSP	No DSP	*p*-Value	DSP	No DSP	*p*-Value	DSP	No DSP	*p*-Value
Sociodemographic									
Age, mean years	38.4, n = 31 (11.9; 19–70)	34.8, n = 105 (9.3; 19–64)	0.075	51.8, n = 21 (18.2; 18–83)	33.2, n = 155 (12.6; 18–84),	< 0.001	43.8, n = 52 (16.0; 18–83)	33.8, n = 260 (11.4; 18–84)	< 0.001
Female Gender	15/31 (48.4)	69/105 (65.7)	0.081	13/21 (61.9)	82/155 (52.9)	0.437	28/52 (53.8)	151/260 (58.1)	0.573
Education (years)	7.1, n = 30 (2.6; 0–12)	7.0, n = 99 (3.6; 0–16)	0.826	5.0, n = 19 (4.2; 0–12),	8.6, n = 153 (3.2; 0–16)	< 0.001	6.3, n = 49 (3.4; 0–12)	8.0, n = 252 (3·4; 0–16)	0.002
Urban Residency	15/31 (48.4)	62/105 (59)	0.293	6/21 (28.6)	69/155 (44.5)	0.240*	21/52 (40.4)	131/260 (50.4)	0.118
Nutrition/food security									
Height, mean cms	162.1, n = 31 (9.8; 144–186)	161.9, n = 105 (10.1; 140–187)	0.920	162.1, n = 21 (11.3; 144–188),	162.3, n = 151 (9.3; 140–186),	0.915	162.1, n = 52 (10.3; 144–188)	162.1, n = 256 (9.6; 140–187)	0.969
Body Mass Index, mean kg/m^2	23.0, n = 31 (3.0; 16.9–28.0)	23.2, n = 105 (3.7; 12.9–32.5)	0.754	23.4, n = 21 (3.0; 16.9–33.3)	23.1, n = 153 (2.8; 11.1–38.1),	0·652	23.2, n = 52 (3.0; 16·9–33.3)	23.1, n = 258 (3.2; 11.1–28.1)	0.970
Skipped a meal due to lack of food††	18/31 (58.1)	56/105 (53.3)	0.642	13/21 (61.9)	71/154 (46.1)	0.174	31/52 (59.6)	127/259 (49.0)	0.164
Went all day without eating due to lack of food††	12/31 (38.7)	29/104 (27.9)	0.250	6/21 (28·6)	41/155 (26.5)	0·837	18/52 (34·6)	70/259 (27·0)	0.268
Takes less meals during dry season	8/31 (25·8)	28/105 (26·7)	0.924	7/21 (33.3)	31/155 (20.0)	0.163	15/52 (28.8)	59/260 (22.7)	0.341
Low dietary diversity**	13/31 (41.9)	21/105 (20.0)	0.013	6/21 (28.6)	34/155 (21.9)	0.496	19/52 (36.5)	55/260 (21.2)	0.017
Food insecure	15/31 (48.4)	43/105 (41.0)	0.462	7/21 (33.3)	46/155 (29.7)	0.732	22/52 (42.3)	89/260 (34.2)	0.267
Weekly alcohol consumption	9/29 (31.0)	18/105 (17.1)	0.099	4/21 (19.0)	22/154 (14.3)	0.523*	13/50 (26.0)	40/259 (15.4)	0.070
Medical									
History of diabetes	2/31 (6.5)‡	0/99 (0)	–	0/21 (0)	1/142 (0.7)	–	2/52 (3.8)	1/241 (0.5)	–
History of TB treatment§	9/31 (29.0)	8/68 (11.8)	0.035	3/21 (14.3)	8/142 (5.6)	0.154*	12/52 (23.1)	16/210 (7.6)	0.001
History of syphilis	11//30 (36.7)	7/64 (10.9)	0.003	3/21 (14.3)	10/141 (7.1)	0.379*	14/51 (27.5)	17/205 (8.3)	< 0.001
Prior metronidazole use	21/31 (67.7)	31/67 (46.3)	0.048	12/21 (57.1)	102/142 (71.8)	0.171	33/52 (63.5)	133/209 (63.6)	0.981
Prior ciprofloxacin use	4/30 (13.3)	1/67 (1.5)	0.031*	1/21 (4.8)	4/142 (2.8)	0.503*	5/51 (9.8)	5/209 (2.4)	0.028*

Data are n/N (%) or mean, n (SD; range); χ^2 for categorical variables and Student's *t*-test for continuous variables unless otherwise indicated.
† n = 312 (two participants with two signs of DSP who did not meet the study definition of DSP excluded).
* Fisher's Exact Test.
** Estimated from monthly maize flour consumption per adult equivalent unit in household.
‡ only one DSP case confirmed to have diabetes while one had a normal HbA1c despite lack of taking a glucose lowering medication.
†† Refers to last 7 days.

Table 4
Multivariate logistic regression model of participant characteristics associated with DSP.[a]

Characteristic	Bivariate analysis OR (95% CI)	Full model OR (95% CI)	*p*-Value
Site	0.68 (0.36–1.22)	0.53 (0.22–1.32)	0.132
HIV	2.18 (1.19–4.00)	3.8 (1.74–8.30)	0.001
Age (years)	1.06 (1.03–1.08)	1.06 (1.03–1.09)	< 0.001
Education (years)	0.88 (0.80–0.96)	0.91 (0.81–1.02)	0.093
Low Dietary Diversity	2.12 (1·10–4·15)	1.75 (0.80–3.82)	0.234
History of Tuberculosis	3.42 (1.52–7.72)	1.26 (0.44–3.61)	0.776
History of Syphilis	4.18 (1.90–9.22)	2.08 (0.79–5.48)	0.129
History of Metronidazole Use	0.92 (0.53–1.87)	1.79 (0.77–4.15)	0.174
History of Ciprofloxacin Use	4.44 (1.23–15.95)	8.82 (1.67–46.76)	0.010

Full Model: Presence of DSP (yes = 1) = site (urban) + HIV + age + education +low dietary diversity + history of tuberculosis + history of syphilis + history of metronidazole use + history of ciprofloxacin use; OR = odds ratio, CI = Confidence Interval.

[a] Full model sample size includes 251 participants, of which 48 were cases.

(n = 6) of HIV− cases had borderline low levels. Among 40 DSP cases with both investigations available, two of 24 (8.3%) HIV+ and one of 16 (6.3%) HIV− cases had low or marginally low levels of both vitamin B12 and erythrocyte folate ($p = 1.000$). Reactive RPR was seen in 12.5% (n = 3) of HIV+ and 11.8% (n = 2) of HIV− DSP cases. No cases of hypothyroidism were identified. Forty-two (81%) DSP cases had available HbA1c results. Diabetes mellitus was confirmed in only one (2.3%) HIV+ case with known diabetes, while another participant was thought to have an HbA1c falsely elevated secondary to hemoglobinopathy. Two (8.0%) HIV+ and two (11.8%) HIV negative DSP cases had impaired glucose tolerance. Uremia was not identified in any DSP cases.

5. Discussion

5.1. DSP prevalence

The DSP prevalence rate of 22.6% (95% CI 18.5–26.7%) in our study among HIV+ participants without neurotoxic ART exposure is similar to the 11–33% prevalence rates reported in other studies from SSA in which DSP is defined by a combination of signs and symptoms [14–18]. Since 70% of our HIV participants were presenting with a new diagnosis and were ART-naive, our findings may not be generalizable to a broader spectrum of HIV−treated populations. However, there was no difference in DSP prevalence among ART-treated individuals in our study. A similar DSP prevalence of 18% was also seen among HIV+ South Africans after 24 months of ART treatment [19].The most recent studies of HIV populations outside Africa using a case definition requiring both signs and symptoms have reported prevalence rates of only 2–4% [20,21]. The seemingly disproportionate burden of HIV-associated DSP prevalence in SSA compared to those recently reported from the U.S. may be at least partially explained by ART access differences, with patients from SSA being more immunosuppressed for longer periods of time prior to receiving ART [22]. HIV care guidelines in Zambia at the time of this study supported ART initiation when CD4 counts were < 350 cells/mL or HIV clinical stage was advanced- and advanced HIV disease is still frequently associated with DSP [21,23]. Further, our study found significant associations between nutritional characteristics and neurotoxic drug exposures in HIV+ participants, which may also explain the widening prevalence gap, and demonstrates the selective vulnerability to neuropathic injury that is present with HIV infection. We previously reported a 75% prevalence rate of DSP symptoms in ART-naïve participants recruited from the same rural site in 2006–2007 [1]. Neurologist-performed assessments of DSP signs and symptoms, which were not performed in our prior study, likely improved diagnostic specificity and resulted in a lower prevalence rate. Further, the HIV cohort enrolled in our prior study may have been living with HIV for decades without access to treatment before 2004. Temporal changes in the medical and socioeconomic characteristics of these HIV populations may also have contributed to decreased prevalence of DSP in the present study.

No population-based DSP prevalence estimates outside the context of HIV are available from SSA. In Guinea-Bisseau, 7% of VCT attendees were found to have DSP compared to 12% in our study [24]. Estimates of VCT attendees may inflate prevalence rates, as patients with DSP may be referred to VCT for HIV testing. However, a recent study from rural Uganda reported a similar 11% prevalence of symptomatic DSP in a community-based study [25]. These rates are excessive compared to other world regions, where symptomatic DSP prevalence in the general population is estimated at only 1–3% and warrant further study [26,27].

Prior studies of HIV+ populations frequently define DSP by the presence of one abnormal neurological exam sign evident bilaterally, termed asymptomatic DSP. In our study, 46.5% of HIV− participants were noted to have such findings on neurologist-performed assessments, emphasizing the questionable diagnostic validity of this definition for HIV-associated DSP in this setting. A 20% prevalence of asymptomatic DSP signs was also seen in the aforementioned study of HIV negative community-based study participants in rural Uganda [25]. In our study, rural residency appears to be an important factor associated with asymptomatic DSP even after controlling for baseline differences in age, education, height, and HIV status. It is difficult to exclude the possibility that inter-site differences in language, cultural factors, or examination techniques influenced our results. However, both study teams have > 10 years of medical research experience and trained together to limit variability in interview procedures between sites. Similarly, both study neurologists were present for one third of the recruitment period at the rural site to maximize consistency in exam procedures.

Understanding the significance of the high rates of asymptomatic signs outside the context of HIV, as well as association with rural residency, requires further study. The significance of asymptomatic DSP signs is unclear. In a large HIV cohort study from the U.S., asymptomatic signs increased in frequency over time but did not predict incident symptomatic DSP in HIV patients after 36 months of follow-up [28]. In a recent longitudinal study of HIV+ patients starting ART in South Africa, a non-significant trend toward symptomatic DSP was observed after 24 months of treatment [19]. The authors of this study and others postulate that the increasing prevalence of DSP signs over time in ART-treated patients results from mitochondrial dysfunction and slowed axonal transport [19,29]. Given our findings and those recently reported from rural Uganda, if nutritional or environmental challenges during a critical developmental period negatively impact peripheral nervous system health later in life deserves consideration [30].

5.2. Factors associated with DSP

5.2.1. Sociodemographic characteristics

We found that older age and low educational ascertainment were associated with DSP among HIV negative participants. Older age is a well-established risk factor for HIV neuropathy as well as DSP due to other causes [31–34]. Low education, poverty and low income have all been previously associated with DSP in other studies [1,2,35]. We hypothesize that low educational ascertainment is a marker of early childhood deprivation. Early childhood deprivation is associated with an increased risk of a broad range of other adult onset diseases as well as altered brain structure and development [36,37].

5.2.2. Non-ART neurotoxic medication exposures

Metronidazole and ciprofloxacin exposures were associated with

DSP among HIV+ persons in this study. Metronidazole is rarely associated with DSP in clinical practice in developed country settings. A recent systematic review found the highest DSP risk among patients requiring high doses (> 42 g) or prolonged courses (≥ 4 weeks) [38]. Unfortunately, we were unable to capture prescribing characteristics in our study. Of note, 63.6% of our study participants reported previously taking metronidazole. As such, HIV clinicians in the region should inquire about current metronidazole use and the temporal relationship to onset of symptoms in patients presenting with DSP given that it is a very common exposure, alternative treatments may be available, and DSP symptoms may be reversible with discontinuation. The association between DSP and metronidazole exposure may also be a proxy measure for nutritional deficiencies associated with chronic diarrhea, malabsorption or inflammatory bowel disease.

Ciprofloxacin use was associated with DSP in HIV+ patients and also remained highly associated with DSP presence in the multivariate logistic regression model. Floroquinolones are recognized to increase DSP risk in other populations [39].

Others have previously reported an increased DSP risk associated with a history of tuberculosis treatment [16]. In our study, we were unable to assess if participants received pyridoxine at the time of TB treatment initiation. In HIV+ South Africans on anti-tuberculosis treatment, a heightened risk of DSP remained despite active symptom-based pyridoxine dose adjustments and monitoring of plasma pyridoxal 5′-phophate to ensure adequate supplementation, suggesting that isoniazid-associated pyridoxine deficiency alone does not entirely explain the excess risk [40].

The associations between DSP, metronidazole, ciprofloxacin, and history of tuberculosis treatment should be interpreted with caution given a number of limitations in our study. Very few charts were available for abstraction, and we cannot exclude the possibility of a recall bias among DSP cases. However, some of these exposures, such as ciprofloxacin and metronidazole, are readily available over the counter in Zambia and relying solely on chart data may also miss a substantial number of medication exposures. Some of these exposures, such as ciprofloxacin, were also quite rare in our study and a chance association with DSP cannot be excluded.

5.2.3. Medical history and co-morbid disorders

Compared to other world regions, diabetes was uncommon amongst our DSP cohort with only one (2.3%) case with comorbid HIV identified. An additional four (9.5%) cases had impaired glucose tolerance, a condition associated with increased risk of DSP in other populations [33,41]. The low rate of diabetes in our cohort may be partially explained by the relatively young age, low rates of obesity, and predominance of ART naïve participants in our study. However, diabetic phenotypes are not well delineated in SSA and pathophysiologic mechanisms and also complications may differ from those in high-income countries [42].

A strong association between a history of syphilis and HIV+ DSP cases was an unexpected finding and did not remain significant in the multivariate model. Diagnosis of syphilis is entirely based on RPR findings in this setting without routine availability of more specific diagnostic tests. False positive RPR has been associated with a number of conditions that are also associated with DSP, such as systemic lupus erythematous and Hepatitis C-associated cryoglobulinemia, among others [43,44]. Unfortunately, we were unable to test for these conditions in our study.

5.2.4. Dietary and nutritional characteristics

We found the odds of DSP were increased nearly 3-fold in HIV+ persons belonging to a household with low dietary diversity regardless of urbanicity. Unlike our prior study in rural Zambia, which defined food security based upon taking fewer meals in the months prior to annual maize harvest, we did not find an association between food security and DSP in HIV+ participants. However, inadequate nutrient intake associated with the unvaried, cereal-based diets common to many countries in SSA may be more relevant in an urban population. Micronutrient deficiencies have been shown to be extremely common in the context of HIV, possibly secondary to decreased intake, higher metabolic demand, and/or increased losses associated with malabsorption [45]. HIV infection itself has been implicated as a potential cause of gastric hypochlorhydria, a known risk factor for vitamin B12 deficiency, although the mechanism remains undefined [46].

Low erythrocyte folate and vitamin B12 levels were common in our DSP cohort. As these assessments were performed only in participants with DSP, we do not know whether these findings contributed to the presence of DSP. Vitamin B12 deficiency presenting as DSP or small fiber neuropathy has been previously reported [47]. The significance of low serum vitamin B12 in HIV is controversial. Some studies have indicated a non-physiologic decrease in serum measurements with advancing HIV infection and decreased levels of circulating haptocorrin, a cobalamin binding protein secreted by neutrophils [48]. However, in our study low serum vitamin B12 and erythrocyte folate levels were even more common among HIV negative DSP cases.

5.3. Conclusions

Complex relationships between HIV, poor nutrition, and neurotoxic drug exposures exist in persons with DSP in SSA. Neurotoxic drug exposures such as metronidazole and ciprofloxacin are potentially avoidable or reversible etiologies of DSP. Clinicians in sub-Saharan Africa should query patients presenting with DSP for recent use of these medications and consider discontinuation or alternative treatments when possible. Nutritional neuropathies may also be common causes of DSP. Further studies are needed to better delineate the role of specific micronutrients deficiencies, particularly on the spectrum of neurological complications associated with HIV. The clinical overlap between the neurological manifestations of micronutrient deficiencies and those of HIV make definitive diagnosis challenging. Micronutrient deficiencies are highly responsive to treatment when the diagnosis is expeditious, but frequently lead to irreversible neurological disability when treatment is not immediately rendered. Thus, the stakes of misdiagnosis are high with treatment being relatively inexpensive. The role of specific micronutrients in the pathogenesis of DSP and other neurological disorders among HIV+ patients deserves urgent appraisal in areas where high prevalence of malnutrition and HIV intersect.

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Appendix A. Supplementary data

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