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Peripheral neuropathy in HIV patients on antiretroviral therapy: Does it impact function?

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ABSTRACT

HIV-associated distal sensory polyneuropathy (DSP), with or without neuropathic symptoms, can develop after anti-retroviral therapy (ART). Symptoms frequently involve small fibres but reports on autonomic dysfunction in HIV-DSP are sparse. We studied an HIV-infected cohort after 5 years of ART, and report on the frequency and severity of autonomic symptoms and the impact of DSP on everyday function. This cross-sectional study comprised of participants from a community-based South African HIV-clinic. The Brief Peripheral Neuropathy Screen and reduced Total Neuropathy Score evaluated neuropathic symptoms/signs. DSP was defined as ≥2 symmetrical DSP-signs, and symptomatic DSP when accompanied by neuropathic symptoms. Autonomic symptoms questionnaires, heart rate variability and postural blood pressure changes were assessed. The Lower Extremity Functional Scale (LEFS) was completed. The 67 participants had a median age of 42 years and median ART exposure of 7 years with viral suppression in 84%. Most (81%) met our criteria for DSP and 36% had additional neuropathic symptoms. Autonomic symptoms and signs (above normative values) were present in 15% and more likely in those with symptomatic DSP ($P < .001$). Participants with DSP, even without symptoms, had lower LEFS scores ($P \leq .039$) than those without. HIV-DSP is prevalent and impacts on daily living.

1. Introduction

HIV-associated distal sensory polyneuropathy (DSP) can manifest clinically either before or after the initiation of antiretroviral therapy (ART) [1]. DSP associated neuropathic symptoms arising after the initiation of ART, are more likely to occur within the first 3 to 6 months of starting ART and this risk is higher if the individual has previously been, or currently receiving treatment for tuberculosis [1–4]. Neuropathic symptoms include: symmetrical numbness, burning sensation, and stabbing pain in the feet. However, DSP without symptoms is more prevalent. In contrast to symptomatic DSP, asymptomatic DSP has been found to insidiously increase in prevalence in both an African cohort which was followed over the first 2 years after ART initiation [6], and in a large North American cohort over several years of observation [5]. Although studies based on self-reported neuropathic symptoms in HIV-infected participants, both from the United States and Rwanda, found that the quality of life of subjects was significantly lower in those with neuropathic symptoms [7,8], there is little data about the functional impairment of those who are affected by asymptomatic DSP. One of the questions we aim to answer in this study, which is particularly relevant in Sub-Saharan Africa where the disease burden is the highest [1], is: Does the accrual of neuropathic signs in HIV-infected individuals on ART for several years impact their daily function?

Although HIV-DSP is characterized by signs of small fibre dysfunction with increasing loss of pin sensibility in a length-dependent manner, in addition to large fibre dysfunction [6,9], there are few studies enquiring about autonomic dysfunction in these individuals. Early studies showed autonomic dysfunction in patients with advanced HIV infection [1]. However, more recently, evidence of autonomic dysfunction was found in 61% of HIV-positive patients in a North American cohort, of whom 95% were on ART [10]. Notably, diabetes was present in > 10% in that older cohort and many admitted to use of

Abbreviations: DSP, distal sensory polyneuropathy; ART, anti-retroviral therapy (ART); HIV, Human Immune Deficiency virus; AIDS, Acquired immune deficiency syndrome; LEFS, Lower Extremity Functional Scale; BPNS, Brief Peripheral Neuropathy Screen; TNSr, reduced version of the Total Neuropathy Score; SAS, Survey of Autonomic Symptoms; TIS, total impact score; BP, blood pressure

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concomitant medications for cardiovascular-related comorbidities and previous illicit drugs, which are all factors that differ from African cohorts. In a smaller, younger, and predominantly male sample from Hawaii, autonomic symptoms amongst those on ART were four times more frequent compared to HIV-negative controls, but neuropathy status was not assessed [11]. Therefore, in this study our aims were a) to assess the frequency and severity of neuropathy and autonomic dysfunction in HIV-infected South Africans after at least 5 years of ART and b) the relevance and effects of having neuropathic signs on an individual's daily functioning using a validated functional scale.

2. Methods

2.1. Study design and population

Ambulant, HIV-positive adults from a community health care centre in Crossroads, Cape Town, and who had previously participated in cross-sectional studies [3,12], were invited to participate. Subjects were eligible if they were on ART for at least 5 years and were clinically well i.e. without an active opportunistic infection or anti-tuberculosis therapy of < 1 month duration, or active alcohol or substance misuse. All participants provided written informed consent prior to assessment. This study was approved by the University of Cape Town Research Ethics Committee (HREC REF 221/2008).

2.2. Participant assessment

These were conducted over 2 consecutive days as previously described [13]. A comprehensive medical history of participant habits, comorbid disease, prior tuberculosis and current medication (including ART) usage was taken. Patient demographics, height, weight and waist circumference were recorded.

A focussed neuropathy examination was performed by a clinician and supervised by a neurologist (JMH). This included the Brief Peripheral Neuropathy Screen (BPNS) and a reduced version of the Total Neuropathy Score (TNSr) as previously described [3,6]. The sensory symptoms evaluated by the BPNS (in English and isiXhosa) included symmetrical neuropathic pain, numbness and “pins-and-needles” and graded on a numerical rating scale (NRS) from 0 to 10. Vibration sensibility at the terminal hallux (using a 128 Hz tuning fork) and ankle tendon reflexes, comprise the examination domains evaluated by the BPNS. The TNSr assessed the distal to proximal extent of sensory symptoms, pin sensibility, vibration sensibility, deep tendon reflexes and muscle strength in a quantitative fashion from 0 to 4 (symptoms/signs extending above knees/elbows). Proprioception was assessed at terminal hallux as normal, reduced (> 2/10 mistakes) or absent [6].

For the purposes of this cross-sectional analysis, DSP was defined as the presence of any two neuropathic signs in a distal and symmetrical distribution, and symptomatic DSP, when accompanied by any neuropathic symptoms in a distal symmetrical distribution. Patients were classified as asymptomatic if they have DSP without any symptoms.

The Lower Extremity Functional Scale (LEFS) is comprised of 20 questions that centers on day-to-day lower limb physical ability developed to assess disability in patients with neuromuscular disorders [8]. We translated into isiXhosa a version of the LEFS that had been validated in an African setting and modified to suit the activities of daily living of patients from lower income countries [14]. Each activity is subjectively ranked from 0 (extreme difficulty) to 4 (no difficulty) to attain a total of 80.

The Survey of Autonomic Symptoms (SAS) is a questionnaire [15], which was translated into isiXhosa, that focuses on the presence and severity of autonomic symptoms of the following domains: orthostatic, sudomotor, vasomotor, gastrointestinal, urinary, and male sexual dysfunction. Each item is graded on an impact score ranging from 1 to 5. We used the a priori cut-offs of > 3 autonomic symptoms and a total impact score (TIS) of > 7 to be clinically relevant based on normative controls < 60 years old, as previously published, which showed 90% specificity and 65% sensitivity for determining autonomic dysfunction on the SAS and 90% specificity and 60% sensitivity for autonomic symptom severity as represented by the TIS [15].

Heart rate variability and orthostatic hypotension were measured as described by the Ewing classic battery [16]. Heart rate response to moving from a lying to standing was assessed by measuring the beat-to-beat (R–R) interval change during this change in position. An R-R interval ratio of ≤1.04 was abnormal. Orthostatic hypotension was defined as a drop in systolic blood pressure (BP) of ≥20 mmHg or diastolic BP ≥ 10 mmHg when moving from lying position to standing after 2 min. We also enquired about symptoms of dizziness and palpitations while these measurements were taken.

Each participant had the following blood tests in a fasting state on the second day of testing: oral glucose tolerance test and highly sensitive C-reactive protein (hsCRP). Vitamin B12 levels were subsequently performed in those with severe neuropathy. Recent viral load and CD4 lymphocyte count (within 3 to 6 months of the study visit) were obtained from the national lab results system. Virological suppression was defined as < 400 copies/ml as per the HIV research network [17].

2.3. Statistical analysis

Statistical analysis was performed using Excel, Graph Pad (version 7), OpenEpi (www.openepi.com) and STATA 14.1 (Stata Corp, College Station, Texas). Variables were reported based on their normality; means (± standard deviation (SD)) and medians (interquartile range (IQR)) for normal and skewed data respectively. The difference between proportions was tested using the *Z*-test for proportions. The Student *t*-test was used for continuous, normally distributed variables. The non-parametric Mann-Whitney *U* test was used for group comparisons in skewed continuous variables. Graphical presentation of the different scores was done using Graph Pad. A *p*-value of ≤0.05 was used as the threshold for statistical significance.

3. Results

Sixty-nine participants were enrolled into this study between August 2014 to December 2016, after attempts to make telephonic contact with 150 of those who previously participated in two studies. Fifty were unreachable by telephone. Of the approximately 100 people who were contacted, 19 refused participation, four were ineligible and we were informed of eight deaths. Two of the enrolled participants were subsequently excluded; one had defaulted ART and was abusing alcohol and the other had only been on ART for 2 years. Of the 67 remaining participants one participant did not attend the second day of testing and consequently had missing autonomic data, fasting blood tests and information about the ART regimen.

All participants were black South Africans, 91% were women with a mean age of 42 years. The median time on ART was 7 years and 84% of the participants showed virological suppression defined as < 400 copies/ml. Although the CD4 + nadir was not known in most cases, 39 (58%) had a prior history of tuberculosis. The present ART regimens included: 50 (75%) on tenofovir; 13 (19%) on zidovudine, and 3 (5%) were on stavudine. Fifty-seven (85%) participants had their ART regimen changed due to: convenience of a single pill combination (29), virological failure (13), drug side-effects (10), and pregnancy (1). Four participants could not recall why their ART regimen was switched. Two patients were using cotrimoxazole prophylaxis and 14 received isoniazid prophylaxis, but only six of the latter were taking pyridoxine. Eight patients were taking anti-hypertensive agents; six were on a single agent and two were on 2 agents.

Table 1
Characteristics of participants categorized as having HIV-associated distal sensory polyneuropathy.

Characteristic	Total	DSP 2-signs	No DSP	*p*-Value
	N = 67	*N* = 54	*N* = 13	
Women, N (%)	61 (91)	50 (92.6)	11 (84.6)	0.37*
Age (years), mean (± SD)	41.6 (8.6)	41.8 (8.7)	41.1 (8.5)	0.79ǂ
Previous TB, N (%)	39 (58.2)	32 (59.3)	7 (53.9)	0.72*
BMI (kg/m^2), mean (± SD)	28 (6.3)	27.6 (5.7)	29.9 (8.3)	0.23ǂ
Height (m), median (IQR)	1.59 (1.55–1.63)	1.60 (1.55–1.63)	1.56 (1.55–1.62)	0.42ᵞ
Current CD4 (cells/μL), mean (± SD)	560.2 (236.5)	566.7 (247.1)	536.8 (200.2)	0.69ǂ
Viral suppression, N (%)	56 (83.6)	44 (81.5)	12 (92.3)	0.34*
Viral load < 20 copies/ml, N %	50 (74.6)	38 (70.4)	12 (92.3)	0.10*
ART duration (years), median (IQR)	7 (6–10)	7.5 (6–10)	7 (5–9)	0.22ᵞ
Current D-Drugs, N (%)	3 (4.5)	3 (5.6)	0	0.38*
Isoniazid, N (%)	14 (20.9)	9 (16.7)	5 (38.5)	0.08*

DSP refers to distal sensory polyneuropathy defined as two neuropathic signs; N refers to number, HIV to Human Immunodeficiency virus; SD to standard deviation; TB to Tuberculosis; BMI to body mass index; IQR to interquartile range; viral suppression to < 400 copies/ml; ART to antiretroviral therapy; D-Drugs to dideoxynucleoside reverse transcriptase inhibitor e.g. stavudine; *P*-values derived by *z-test, ǂt-test, ᵞMann–Whitney.

3.1. Frequency and characteristics of DSP

Most (81%) of the participants met our criteria for DSP (two neuropathic signs). Indeed, all participants had at least one symmetrical neuropathic sign on examination. The characteristics of patients with and without DSP are shown in Table 1 and appendix Table A1. There was no difference in the ages between those with and without DSP, nor height measurements, nor previous tuberculosis. There was a trend towards an inverse association between isoniazid as tuberculosis prophylaxis and DSP ($P = .08$), but no associations between the hsCRP levels, metabolic or anthropometric parameters and the presence of DSP.

Overall, sensory symptoms were present in 31 individuals which the participants rated as moderate in severity (4/10) for paresthesiae and 5/10 for burning pain (Table A2). Only four individuals were receiving/taking analgesics. The most common neuropathic signs were decreased pin sensibility and altered deep tendon reflexes, both present in 79%. The median TNSr score was 6 (IQR 4–8) (Fig. 1A).

Symptomatic DSP i.e. two neuropathic signs with symptoms, was present in 36% of the cohort (Table A2). The frequency of neuropathic signs was similar amongst those with and without symptoms. None of the metabolic or anthropometric parameters were associated with the presence of symptomatic DSP (Table A3). Of note, altered proprioception sense was present in 40% and because of this high frequency, we measured serum vitamin B12 in those with impaired proprioception, but all had values within the normal laboratory reference range (mean serum vitamin B12 amongst 26 patients with impaired proprioception = 365 pmol/L; standard deviation (SD) ± 127.3; normal > 138 pmol/L).

As the frequency of DSP was so high, an analysis using a more stringent definition for DSP (≥3 signs), showed a trend towards previous tuberculosis being more common in those with DSP-3 signs (68 vs. 47%, $P = .085$).

3.2. Autonomic dysfunction

A majority ($n = 40$, 60%) of the cohort had either a positive response on the autonomic symptom survey (SAS > 3, Fig. 1B, and/or TIS > 7, Fig. 1C) or cardio-autonomic signs of abnormal heart rate variability ($n = 16$) and orthostatic hypotension ($n = 10$). Ten (15%) had a combination of more frequent and severe autonomic symptoms compared to control data [14] with positive SAS (> 3) and TIS (> 7) and abnormal cardio-autonomic signs.

Overall, those with DSP had a median SAS score of 2 (IQR 1; 4) and TIS of 6.5 (IQR 2; 10.8) implying that many had ≤3 symptoms (Table A4), and was therefore regarded as non-specific, most frequently lightheadedness and cold feet (Table 2). Although erectile dysfunction was present in three of six men, it was deemed non-specific in two with only one man having > 3 autonomic symptoms. The presence of DSP did not correlate significantly with the presence or severity of autonomic symptoms or abnormal heart rate variability, but there was a trend towards an association with postural hypotension ($p = .09$). Only two participants had diabetes, one of whom had autonomic symptoms and signs. Two individuals with postural hypotension were taking anti-hypertensive medication and two were on tricyclic agents for painful neuropathy.

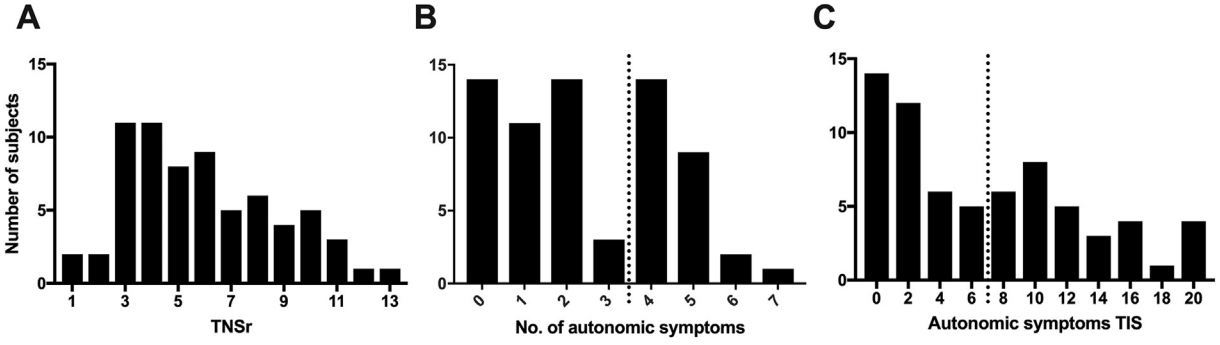

Fig. 1. Distribution of the total neuropathic scores and the autonomic symptoms scores.
A. Histogram of the total neuropathic score (TNSr) by number of subjects. The total score (maximum 20) represents the anatomical extent of the 5 categories of symptoms and signs. B. Number of autonomic symptoms using the screen for autonomic symptoms (SAS); y-axis refers to the number of subjects. C. The total impact severity score (TIS) is a measure of severity of each autonomic symptom. In B, C the dotted line represents the control (< 60 years) cut-off as described in methods. y-axis refers to the number of subjects.

Table 2
Frequency and severity of autonomic symptoms amongst the total cohort.

Autonomic symptom	Frequency, N (%)	Severity, median (IQR)
Light headedness	33 (49)	3 (2–3)
Dry mouth/dry eyes	17 (25)	2 (1–2)
Blue or pale feet	12 (18)	3 (2–4)
Colder feet	26 (39)	4 (2–5)
Decreased sweating in feet	14 (21)	2 (1–2)
Decreased/absent sweating in feet after exercise	13 (19)	2 (1–2)
Increased sweating in hands	6 (9)	2 (1–2)
Nausea, vomiting, bloating after small meal	14 (21)	2 (2–3)
Persistent diarrhoea	5 (8)	2 (1–3)
Persistent constipation	16 (24)	2 (1–4)
Urinary incontinence	9 (1)	2 (1–3)
Erectile dysfunction (men)	3	4 (3–5)

Each symptom is scored on severity scale from 1 (mild) to 5 (severe). N refers to number; IQR refers to interquartile range.

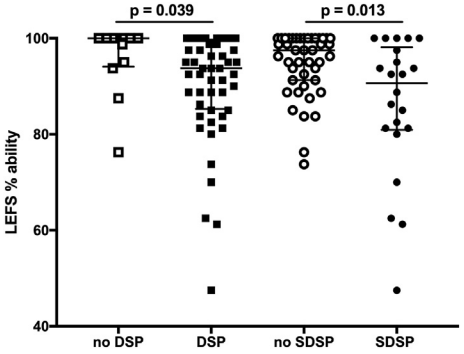

Fig. 2. Scatter plot depicting the lower extremity functional scores (LEFS) by neuropathy status.
The LEFS % ability reflects the LEFS score as percentage where 100% is full ability with all tasks. DSP refers to 2 neuropathic signs ± symptoms and SDSP reflects DSP with neuropathic symptoms. Medians and interquartile ranges are reflected.

There was a trend towards participants with symptomatic DSP compared to those without symptoms reporting twice as many autonomic symptoms (median 4 vs 2; $P = .081$), and they experienced greater severity of their autonomic symptoms (median TIS 10 vs 3; $P = .005$)(Table 3). The severity of autonomic symptoms (TIS), but not the number of autonomic symptoms, correlated weakly with TNSr scores ($r = 0.26$; $p = .034$) i.e. distal-to-proximal gradient of neuropathic signs and symptoms. There was a moderate correlation between ART duration and the presence of autonomic symptoms ($r = 0.34$, $P = .002$).

3.3. Lower extremity functional scale associated with DSP and autonomic dysfunction

In order to assess whether the presence of DSP is functionally relevant in a patient's everyday life, 64 participants completed the LEFS questionnaire. Overall the median LEFS score was 93.8% (IQR 85.6; 98.8) for those defined as DSP and 100% (IQR 94.4; 100) for those with < 2 neuropathic signs ($p = .039$; Fig. 2). Those with symptomatic DSP had significantly lower scores compared to those without (88.8% vs. 96.3%; $P = .040$). Furthermore, the LEFS scores correlated stronger with the BPNS score, which grades neuropathic symptoms qualitatively ($r = -0.5$; $p < .001$), compared to the quantitative TNSr ($r = -0.35$; $p = .004$). The autonomic severity scores (TIS) showed stronger inverse correlation with the LEFS ($r = -0.6$; $P < .001$), compared with the number of autonomic symptoms ($r = -0.26$; $P = .034$).

4. Discussion

In this South African cohort of 67 community-based HIV-infected participants, who were mainly women and most of whom could be considered “virologically suppressed” and on ART for 7 years, DSP was common. We found that almost half of the cohort experienced more frequent and severe autonomic symptoms compared to healthy controls younger than 60 [15], in addition to altered cardio-autonomic signs (heart rate variability and postural hypotension). Furthermore, a subset of patients with more extensive neuropathic signs (as measured by TNSr) and symptoms were also experiencing autonomic symptoms of substantial impact (TIS > 7), which added to their morbidity. Nonetheless, the presence of at least two neuropathic signs, even without symptoms, impacted somewhat on the person's everyday function as measured by the lower extremity functional scale.

In this study we were interested in the longer-term consequences of ART in individuals from Africa infected with HIV. More than half of the participants in this study had at least one previous episode of tuberculosis, a known risk factor for developing HIV-associated DSP in this setting, and indicating more advanced HIV disease before starting ART [1,3]. Because of the cross-sectional nature of the analysis, and because most patients had at least one neuropathic sign, we used a more stringent definition of DSP that included two neuropathic signs; we found that 81% of our participants had DSP after at least 5 years of using ART. This is considerably higher than the prevalence of 60% in a similar cohort from the same region, probably with similarly advanced disease, but after only 14 months of ART [3]. However, we do not know the CD4+ nadir of these participants and based on their high frequency of prior concomitant tuberculosis infections, the governmental ART initiation criteria of the time (CD4+ count < 250 cells/μl) and programmatic regimen including stavudine up to mid-2010, it is likely that these participants were at higher risk of developing HIV-DSP than those currently initiating treatment. Nevertheless, we, and others, have shown that asymptomatic DSP in HIV-infected individuals increases longitudinally over time and includes the accrual of small and large fibre dysfunction [5,6]. In addition, although many of the tools used to quantify neuropathic dysfunction in HIV, such as the BPNS and TNSr, do not include proprioceptive dysfunction, we have noted a substantial increase in impaired perception of distal proprioception over time on ART; within the first 2 years of starting ART only 2% had altered distal proprioception at the toes compared to 40% of this group after a median of 7 years on ART [6].

In contrast to the slow accrual of neuropathic signs over time,

Table 3
Autonomic symptoms and lower extremity functional scale by neuropathy status.

Characteristic	Symptomatic DSP $N = 24$	Asymptomatic DSP $N = 30$	*P*-value
Age (years), mean (± SD)	42.5 (10.5)	41.2 (7.1)	0.61[t]
SAS score, median (IQR)	4 (1–5)	2 (1–3.8)	0.081[ɣ]
SAS total impact score, median (IQR)	10 (2.8–15)	3 (2–7.8)	**0.005**[ɣ]
LEFS %, median (IQR)	88.8 (81.3–97.5)	96.3 (90.0–98.8)	**0.038**[ɣ]

DSP refers to distal sensory polyneuropathy defined as two neuropathic signs; N refers to number; SD to standard deviation; SAS to survey of autonomic symptoms; IQR to interquartile range; LEFS to lower extremity functional scale; *P*-values derived by [t]t-test, [ɣ]Mann-Whitney test. Bold refers to statistically significant results.

neuropathic symptoms have been shown in several cohorts to improve after a spike between 3 and 6 months of starting ART and maintaining a stable prevalence from 12 months onwards [2,5,6]. However, in contrast to a previous cohort from this region in which 18% had symptomatic DSP after 2 years of ART [6], here we found, using the same tools, that 36% remained with symptoms after at least 5 years of ART. Although not directly comparable, this cohort had higher frequencies of previous tuberculosis and the participants were older, both of which are recognized as DSP risk factors. Furthermore, even though a viral load of < 400 copies/ml is considered adequate viral suppression [17] there is a trend towards those with < 20 copies/ml associating with less neuropathic signs (Table 1). Taken together, these results suggest that earlier ART initiation and more effective ART program adherence must remain treatment goals to reduce neuropathic complications, although we previously could not detect different incidence signals between previous (stavudine-containing) and present (tenofovir-containing) regimens used in our governmental ART program [6].

We found that the severity of autonomic symptoms experienced by participants with symptomatic DSP added to their morbidity. Few of our patients were on anticholinergics and diuretics and none were on beta- or alpha-blockers which can potentially affect autonomic tests [10]. Although European studies also found reduced heart rate variability in HIV-infected patients on ART, they did not test for postural hypotension [18,19]. While this finding was not common, its presence in our cohort requires a re-evaluation of concomitant medications at the very least.

This study has several limitations which impact on the generalizability of our results. The sample size is small, is cross-sectional and consisted mainly of women (although similar to most African HIV-infected cohorts included in studies) [3,6,20] and the population most likely had a lower CD4+ nadir at ART initiation (as discussed above) than other ART-exposed populations in the developed world. In addition, although autonomic testing was performed in a uniform manner after 8 h of fasting on the second day of testing, the testing protocol was limited. However, the South African governmental ART program adopted the WHO guidelines of 'Test and Treat' towards the end of 2016 and therefore more people are starting on ART earlier in their disease course. Most ART programs in sub-Saharan Africa follow similar ART regimens [21].

5. Conclusion

The frequency and impact of HIV-associated neuropathic symptoms and signs remain high in cohorts who started ART in advanced HIV infection, despite reasonably effective ART after 5 years. Both small and large fibre nerve dysfunction accumulate over time and does appear to impact on an individual's everyday life emphasizing the burden of having HIV-DSP. Early initiation of ART should remain a clinical priority.

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Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.116451.

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