**Abstract**

**Context.** HIV-associated sensory neuropathy (HIV-SN) is a frequent complication of both HIV and neurotoxic antiretroviral medications such as stavudine.

**Objectives.** To determine the prevalence, risk factors, and clinical characteristics of symptomatic HIV-SN in a Black South African cohort of patients exposed to stavudine.

**Methods.** HIV-positive Black South Africans (n = 395) who had received stavudine for at least six months were recruited at the Virology Clinic of the Charlotte Maxeke Academic Johannesburg Hospital, South Africa, and screened for neuropathy using the AIDS Clinical Trials Group neuropathy screening tool. HIV-SN was defined as present if the patient had both symptoms and signs of peripheral neuropathy. If present, the distribution and intensity of symptoms were recorded. In addition, anthropomorphic, demographic, and clinical information were recorded and analyzed as risk factors.

**Results.** The prevalence of symptomatic HIV-SN was 57% (226 of 395). Increasing age and height were independently associated with the development of SN among patients who had used stavudine. Pain was the primary symptom reported by participants with HIV-SN (76%, 172 of 226), followed by numbness (48%, 108 of 226), and pins and needles (46%, 105 of 226). About three-quarters of participants rated their symptoms as being of moderate to severe intensity. Symptoms were always present in the feet and only 23% experienced symptoms proximal to the feet.

**Conclusion.** HIV-SN was common in this population and frequently associated with moderate to severe pain in the feet. HIV-SN was significantly associated with increasing age and height, factors that could be measured at no added cost prior to stavudine prescription, allowing higher risk patients to be offered priority...
Introduction

HIV-associated sensory neuropathy (HIV-SN) affects quality of life and ability to work, and is a well-documented complication of HIV infection. Since the introduction of antiretroviral therapy (ART), the incidence and prevalence of HIV-SN has increased. This increase has been linked to the use of ART regimens containing particular nucleoside reverse transcriptase inhibitors, notably stavudine. Despite the World Health Organization recommending use of stavudine be phased out, stavudine-based treatment programs continue to be introduced and expanded in many countries because of lack of cost-effective alternatives, so stavudine-related toxicities are expected to increase.

The aim of the study was to determine the risk factors for HIV-SN in a Black South African cohort with universal exposure to stavudine. We aimed to characterize the intensity and distribution of three common symptoms of peripheral neuropathy—pain, numbness, and pins and needles—to establish the symptom experience of HIV-SN. We also aimed to create a risk profile for individuals likely to develop HIV-SN after starting stavudine-based therapy to guide clinicians’ prescription choices. This work is critical. Although access to alternative HIV treatments remains limited in this region, the only way to reduce the impact of stavudine toxicity is to understand which patients are at highest risk and offer these individuals priority access to alternative regimens.

Methods

Participants

HIV-positive adults who had used stavudine for at least six months were screened for neuropathy at the Virology Clinic of the Charlotte Maxeke Johannesburg Academic Hospital, South Africa, between July 2008 and April 2009. The study was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, South Africa (protocol number: M080220), and written, informed consent was obtained from all participants. An interpreter fluent in English and all local African languages facilitated consent and study procedures.

Procedures

Participants were screened using the AIDS Clinical Trials Group Brief Peripheral Neuropathy Screen. Participants were considered to have symptomatic HIV-SN if they had at least one symptom (pain, aching, burning, numbness, or pins and needles) and at least one clinical sign of neuropathy (reduced vibration sense or absent ankle reflexes) in each leg. Vibration sense was assessed using a 128 Hz tuning fork, which was placed on the interphalangeal joint of each great toe; vibration sense of 10 seconds or less was considered abnormal. If participants acknowledged the presence of symptoms, the anatomical distribution and intensity of the symptoms were recorded. Symptom intensity was rated on an 11-point rating scale anchored at “0” (no symptom experienced) to “10” (worst imaginable). Pain was classified as moderate to severe with a score of four or greater on this scale.

Demographic (age, gender, ethnicity) and clinical information (current and nadir CD4 T-cell counts, duration of HIV infection, AIDS-defining illnesses), antiretroviral treatment history, and other potential causes of neuropathy (diabetes mellitus, alcoholism, vitamin B12 deficiency, exposure to isoniazid and chemotherapy) were obtained through participant self-recall and their medical files. Participants’ heights and weights were recorded and a venous blood sample was taken for hepatitis C serology (Abbott AxSYM HCV version 3.0 microparticle enzyme immunoassay, Abbott Laboratories, Abbott Park, IL).
Statistical Analyses

Normally distributed continuous data are presented as mean (SD), and nonparametric data as median (range). Univariate analyses of risk factors associated with neuropathy were undertaken using Chi-squared tests (dichotomous variables), unpaired t-tests (parametric continuous variables), and Mann-Whitney tests (nonparametric continuous variables). Multivariate analysis was performed using multiple logistic regression modeling with a reverse selection procedure. Variables were included in the model if they had previously been associated with HIV-SN or if they were associated with SN (P < 0.1) in the present study. The variable least strongly associated with SN was then removed in a stepwise fashion until the removal of any more variables substantially impaired the resulting model. Receiver operating characteristic (ROC) analyses were used to determine cutoff values for continuous variables that were associated with neuropathy in this cohort that provided optimum diagnostic efficiency of HIV-SN. That is, cutoffs that provided the best levels of sensitivity and specificity when categorizing individuals into higher and lower HIV-SN risk groups were chosen.

Results

Three hundred and ninety-five patients participated in the study, of whom 226 (57%) had a clinical diagnosis of symptomatic HIV-SN. All participants identified themselves as Black Africans, were 18 years or older, had a confirmed HIV infection, and had been on stavudine-based ART for at least six months.

Demographic and Clinical Data

Demographic and clinical data are shown in Table 1. Non-HIV-related neuropathy risk factors such as diabetes were uncommon. Hepatitis C testing of the first 300 participants showed no association with HIV-SN. Nadir CD4 T-cell counts were not available for 18 participants who had commenced antiretroviral treatment at other clinics. Although 24% (n = 96) of participants had been exposed to stavudine at a dose of 40 mg twice daily, no participant was receiving more than 30 mg stavudine orally twice daily at the time of screening. No patients had been prescribed a protease inhibitor or zalcitabine.

Prevalence and Characteristics of HIV-SN

In addition to the 226 (57%) patients with symptomatic HIV-SN, 25% (n = 97) had either symptoms or signs of neuropathy, but not both. Pain was the symptom most often reported by participants diagnosed with symptomatic HIV-SN (76%, 172 of 226) (Table 2). Seventy-four percent (128 of 172) of participants with pain, 76% (82 of 108) of participants with pins and needles, and 77% (81 of 105) of participants with numbness reported experiencing the symptom at moderate to severe intensity. Thirty-nine percent (89 of 226) reported two or more symptoms. All participants with HIV-SN experienced symptoms in their feet. Pain proximal to the feet was reported by less than half of those with pain.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-SN (symptoms and signs)</td>
<td>226 (57)</td>
</tr>
<tr>
<td>Symptom prevalence in HIV-SN</td>
<td></td>
</tr>
<tr>
<td>Pain, aching, or burning</td>
<td>172 (76)</td>
</tr>
<tr>
<td>Pins and needles</td>
<td>105 (46)</td>
</tr>
<tr>
<td>Numbness</td>
<td>108 (48)</td>
</tr>
<tr>
<td>Sign prevalence in HIV-SN</td>
<td></td>
</tr>
<tr>
<td>Reduced vibration sense</td>
<td>99 (44)</td>
</tr>
<tr>
<td>Absent ankle jerks</td>
<td>191 (85)</td>
</tr>
</tbody>
</table>
**Risk Factors Associated with HIV-SN**

Increasing age \((P<0.001)\) and increasing height \((P=0.005)\) were the only factors significantly associated with HIV-SN on univariate analyses (Table 3). Factors included in the multiple regression model were 1) age, height, didanosine exposure, and a history of an AIDS-defining illness (based on \(P<0.1\) on univariate analysis), and 2) a history of an AIDS-defining illness, nadir CD4, diabetes mellitus, or isoniazid use (based on associations with HIV-SN in other cohorts).\(^4,14,16\) The only factors independently associated with neuropathy risk among stavudine-exposed African HIV patients were age and height (Table 4).

ROC analysis comparing age and neuropathy status in all 395 participants yielded an area under the curve (AUC) of 0.66 (95% confidence interval [CI]: 0.61–0.72). An age cutoff of \(\geq 38\) years had a sensitivity of 68% and a specificity of 63% for predicting neuropathy. When comparing height and the presence of neuropathy with ROC analysis, the AUC was 0.59 (95% CI: 0.33–0.65), and a height cutoff of \(\geq 158\) cm had a sensitivity of 64% and a specificity of 51% for predicting neuropathy. When age and height were combined, the prevalence of neuropathy was 35% in younger, shorter participants and 76% in older, taller participants (Table 5).

**Discussion**

We identified risk factors, created a risk profile, and described the symptom experience of symptomatic HIV-SN in a stavudine-exposed cohort of South African patients. Patients most likely to develop a symptomatic HIV-SN after stavudine exposure may now be identified and the expected severity of their symptoms better understood. The prevalence of symptomatic HIV-SN was 57%, showing this is a common problem in African patients exposed to stavudine-based ART. Importantly, three-quarters of individuals with HIV-SN reported moderate to severe pain demonstrating substantial suffering. Age and height were the only independent risk factors associated with HIV-SN in our cohort. Although these factors do not explain all the variation in SN status following stavudine exposure (model \(r^2 = 0.07\)), simple stratification of patients by age (\(\geq 38\) years) and height (\(\geq 158\) cm) can predict those at highest risk for HIV-SN (Table 5). HIV-SN is, therefore, a clinically important condition and efforts to reduce the incidence of new cases of HIV-SN are critical, particularly in clinics where stavudine use continues.

Routinely recording age and height are quick and easy tasks that can be part of a normal patient assessment, and our finding that risk of symptomatic HIV-SN increases with increasing age and height, across all ages and heights, has important clinical implications. In any setting where the use of stavudine is an economic necessity, we suggest that priority access to less toxic antiretroviral agents should be given to older and taller (and particularly both older and taller) patients. In this way, rates of SN are likely to be reduced. Improved patient and doctor awareness of HIV-SN and

### Table 3

**Univariate Associations Between HIV-SN Status and Demographic/Clinical Variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>SN Free ((n = 169))</th>
<th>SN ((n = 226))</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>128 (76%)</td>
<td>167 (74%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Age (years)</td>
<td>36.4 ± 7.6</td>
<td>40.8 ± 8.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>157.6 ± 8</td>
<td>160.1 ± 8</td>
<td>0.003</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.2 ± 13</td>
<td>69.6 ± 14</td>
<td>0.3</td>
</tr>
<tr>
<td>Months since HIV diagnosis</td>
<td>45 (6–204)</td>
<td>46 (7–240)</td>
<td>0.4</td>
</tr>
<tr>
<td>Current CD4 T-cell count</td>
<td>386 (45–1079)</td>
<td>380 (27–1091)</td>
<td>1.0</td>
</tr>
<tr>
<td>Nadir CD4 T-cell count</td>
<td>96 (2–403)</td>
<td>91 (1–253)</td>
<td>0.7</td>
</tr>
<tr>
<td>AIDS-defining illness</td>
<td>68 (40%)</td>
<td>108 (48%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Tuberculosis (isoniazid use)</td>
<td>65 (38%)</td>
<td>95 (42%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Hepatitis C seropositivity</td>
<td>4 (2%)</td>
<td>5 (2%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Didanosine ever</td>
<td>11 (7%)</td>
<td>26 (12%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (2%)</td>
<td>8 (4%)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Dichotomous variables are shown as number (%) and compared with SN status using a Chi-squared test. Normally distributed variables are shown as mean ± standard deviation and compared with SN status using an unpaired t-test. Nonnormally distributed continuous variables are shown as median (range) and compared with SN status using a Mann-Whitney U test.
increased frequency of follow-up of patients at risk of HIV-SN also may facilitate prompt regimen revision if neuropathy symptoms develop. Early switching off stavudine when neuropathy develops may improve the likelihood of symptom resolution.17,18 However, although the cutoff values for age and height identified using ROC analysis provide the optimum predictive efficiency for HIV-SN in the cohort studied, precise cutoffs will vary by population4 and they should not be adopted more broadly. Rather, they are provided to illustrate the important point that older, taller individuals are at increased risk of developing HIV-SN.

It is worth noting that 57% of patients presented with symptomatic HIV-SN despite most patients only ever having been exposed to twice daily 30 mg doses of stavudine. Treatment guidelines worldwide have changed to reflect the reduced toxicity of 30 mg rather than 40 mg stavudine doses.19 However, our data show an unacceptably high prevalence of HIV-SN, even among patients exposed to this “less toxic” dose. Makinson et al.20 recently reported the effectiveness of 20 mg doses of stavudine. Although stavudine use is due to be phased out,9 this will take time as there are few cost-effective alternatives.11 Should the effectiveness of 20 mg doses be confirmed and if the safety profile of this dosage is more acceptable, use of a 20 mg twice daily stavudine dose should be considered to reduce toxicities while stavudine is being phased out.

Our findings that increasing age and height are associated with increased HIV-SN risk are consistent with several other studies.4,21–24 Indeed, where height has been assessed and found not to be associated with HIV-SN, the diagnosis of “neuropathy” did not require the presence of symptoms.25 We found an association between height and HIV-SN risk despite our cohort being 5 cm shorter on average than other ethnic groups studied,4 and the height cutoff values identified in our cohort through ROC analysis were 12 cm lower. This finding, that height was a risk despite the shorter height of our cohort, may be explained by longer leg length relative to the trunk length in Black compared with White individuals.26 Our findings also confirm that factors associated with HIV-SN in untreated HIV patients such as nadir CD4 T-cell count3 are less important in the context of ART.5,6,24 Lastly, we did not find an association between isoniazid use and HIV-SN in our cohort. Isoniazid is neurotoxic.27 Although coadministration of pyridoxine (as provided to most patients with tuberculosis in our cohort) minimizes the risk of SN,28 isoniazid/pyridoxine use was associated with moderate to severe neuropathy in another African HIV cohort.29 However, in that study, the cohort had not been universally exposed to stavudine. It may be that the greater neurotoxicity of stavudine and the greater exposure to it in our cohort disguised the neurotoxicity of isoniazid/pyridoxine.

Symptoms of HIV-SN are described as following a “glove and stocking” distribution, with the feet being the primary site affected.30 However, the distribution of HIV-SN symptoms is rarely described in the literature. Consistent with earlier reports on HIV-SN symptoms in the pre-HAART era,30 all patients with HIV-SN in our study experienced symptoms in their feet, and over one-third of these patients felt symptoms only in their feet, usually the soles. However, the proximal extension of symptoms above the ankle was greater in our cohort than in untreated HIV-positive patients,30 which may be related to our cohort being exposed to neurotoxic antiretroviral drugs.

The most common symptom experienced in our cohort was pain, with the majority (74%)
experiencing moderate to severe pain. This contrasts with early reports of HIV-SN in untreated patients, where symptoms “were usually mild” and “painful dysethesias were uncommon.”32 This extent and severity of pain observed in our cohort will have a major impact on quality of life and may reduce adherence to antiretroviral drugs.1,33,34

The limitations of this study include that it was cross-sectional. Although this provides an accurate picture of patients attending the clinic currently, we relied on patient recall and data recorded in the medical file to assess risk factors for HIV-SN rather than collecting data prospectively and monitoring for incident cases of HIV-SN. Furthermore, age and height did not fully explain the variation in neuropathy status in our cohort, and, therefore, other factors not measured here also must be important. For example, host genetics may influence HIV-SN risk in patients exposed to stavudine.21,35,36 A study is underway to look at associations between cytokine polymorphisms and SN risk in this cohort. In addition, we used a relatively simple clinical tool to diagnose patients with symptomatic HIV-SN. We have validated this tool against objective measures in the context of HIV infection,13 but it is possible that milder cases of HIV-SN were missed with our chosen diagnostic criteria. In addition, although this tool assesses the major symptoms that have been associated with HIV-SN (pain, pins and needles, and numbness),22,32 our characterization of neuropathy symptoms among African patients exposed to stavudine is limited to the symptoms assessed by this tool.

In conclusion, HIV-SN is a common problem that frequently presents with moderate to severe pain. Patients at highest risk of HIV-SN following stavudine exposure can be identified prior to initiating ART at no extra cost by recording age and height. In resource-limited settings where stavudine frequently still forms the backbone of ART, prioritizing older and taller patients for access to alternative agents could be an effective, inexpensive way to reduce patient suffering.

Disclosures and Acknowledgments

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