Original article

Effects of a reduced dose of stavudine on the incidence and severity of peripheral neuropathy in HIV-infected adults in South Africa

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Background: Although recent World Health Organization (WHO) guidelines recommend withdrawing stavudine (d4T) from first-line antiretroviral therapy (ART), it remains commonly used in resource-limited settings. In 2006, WHO recommended decreasing the dose of d4T from 40 mg to 30 mg to mitigate toxicities. We compared the incidence and severity of peripheral neuropathy by d4T dose in a retrospective cohort study.

Methods: Patients’ charts from an ART-naive population at a rural clinic in KwaZulu-Natal, South Africa, were retrospectively reviewed for signs and symptoms of incident peripheral neuropathy and were graded for severity using the DAIDS scale. Patients enrolled prior to the WHO guideline change were included in the study if they were on d4T 40 mg for ≥ 6 months. After the guideline change all patients were initiated on d4T 30 mg.

Results: A total of 475 patients were analysed, including 235 in the 40 mg cohort (152.7 person-years [py]) and 240 in the 30 mg cohort (244.7 py). Incidence of peripheral neuropathy was 90.4/100 py (95% CI 75.9, 106.8) in the 40 mg cohort versus 40.5/100 py (95% CI 32.9, 49.3) in the 30 mg group (incidence rate ratio 0.45; P < 0.0001). There was no difference in proportion of severe peripheral neuropathy cases (grade 3/4) between the cohorts: 8.3% in the 40 mg group and 8.9% in the 30 mg group (P = 1.0).

In a multivariate analysis, risk of peripheral neuropathy was associated with increasing age (hazard ratio [HR] 1.65, 95% CI 1.24, 2.19), 40 mg dose (HR 2.1, 95% CI 1.61, 2.74) and concurrent tuberculosis therapy (HR 1.41, 95% CI 1.06, 1.87).

Conclusions: Incidence of peripheral neuropathy in the 40 mg cohort was extremely high and, although lower, the rate in the 30 mg cohort was nonetheless unacceptably high.

Introduction

South Africa has the largest population of patients living with HIV/AIDS, with approximately 6 million people infected accounting for 17% of the global burden of HIV infection [1]. In South Africa alone, it is estimated that >1 million people are on antiretroviral treatment [2]. National antenatal HIV seroprevalence studies indicate a prevalence of 30.2% and, in the province of KwaZulu-Natal, prevalence as high as 39.5% [3].

Stavudine (d4T) has been a crucial component of combination antiretroviral therapy (cART) in resource-limited settings due to its affordability and high barrier to resistance. A survey of 23 resource-limited countries found that 70% of patients on first-line cART are on a regimen containing d4T [4]. Despite its therapeutic effect, d4T has an unfavourable side-effect profile that includes peripheral neuropathy, lactic acidosis and lipoatrophy. These clinical toxicities are linked to altered mitochondrial DNA replication. Peripheral neuropathy significantly impairs quality of life, and the incidence of d4T-related peripheral neuropathy prior to dose reduction in patients on a regimen containing d4T is reported to be as high as 56% [5].

The dose-dependent neuropathic effects of d4T were shown in a randomized trial with neuropathy observed in 6% on a dose of 0.5 mg/kg/day, 15% on 1 mg/kg/day and 31% on 2 mg/kg/day [6]. Given this toxicity profile, efforts were made to assess whether a reduced dose of d4T would decrease side-effects, while maintaining viral...
efficacy. Controlled studies have shown that decreasing the dose of d4T from 40 mg to 30 mg twice daily leads to a significant increase in mitochondrial DNA content in peripheral blood mononuclear cells [7] and adipocytes [8], while preserving HIV virological suppression. These studies resulted in the 2006 World Health Organization (WHO) mandate of decreasing the dose of d4T from 40 mg to 30 mg twice daily to mitigate toxic side-effects including peripheral neuropathy. Prior to the guideline change, WHO recommended a dose of d4T 40 mg for patients with bodyweight >60 kg. Patients who weighed <60 kg were started on d4T 30 mg, and if they gained weight would be dose-escalated according to the guidelines [9].

Recent WHO guidelines recommend withdrawing d4T from first-line cART therapy for medications with a more favourable side-effect profile, including tenofovir [10]. South African national guidelines, implemented in April 2010, also mandated a switch to alternative antiretroviral agents; however, the reality of achieving this phase-out of d4T is constrained by high costs and limited supply [11]. Guidelines note that if a patient is tolerating a regimen containing d4T, they should remain on d4T. There are also many resource-limited countries where d4T remains first-line therapy.

As many people will continue on a d4T-based regimen, it is important to optimize the dose of the drug to prevent the development of peripheral neuropathy and other potential dose-dependent toxicities. The aim of this study was to determine if there has been a decrease in incidence and severity of peripheral neuropathy since the dose reduction from 40 to 30 mg and to identify factors associated with a higher risk of developing peripheral neuropathy.

Methods

This was a retrospective cohort study of HIV-infected patients initiated on cART at Vulindlela, the rural outpatient clinic of the Center for AIDS Programme of Research in South Africa (CAPRISA), located in the province of KwaZulu-Natal. Vulindlela is a predominantly Zulu speaking community with a population of approximately 400,000 people. Clinical management of patients is based on the South African Chronic Care Management and Treatment Guidelines for HIV/AIDS, which follow WHO guidelines. Charts were divided into two separate cohorts based on the timing of the government mandated dose reduction. Cohort 1 was enrolled from 2004 and treated with a cART regimen containing d4T 40 mg twice daily for ≥6 months. Cohort 2 comprised patients enrolled at Vulindlela after the dose-reduction strategy was introduced in November 2006 and started on a cART regimen containing d4T 30 mg twice daily. Patients in cohort 1 who had their dose of d4T reduced secondary to decrease in weight <60 kg were not reassigned to cohort 2 and, per the inclusion criteria, had to be maintained on d4T 40 mg for ≥6 months. Furthermore all patients in cohort 1 were censored at the time of the guideline change in November 2006.

Approximately 300 patients per dosing cohort were selected from a cohort of 2,000 patients in care at Vulindlela as follows: patients in cohort 1 were selected consecutively based on treatment initiation date from the dose reduction in April 2006 backwards to June 2004 and patients in cohort 2 were selected consecutively from the dose reduction in November 2006 forwards to April 2009. Patients were excluded if they had a history of prior cART, history of peripheral neuropathy, <6 months follow-up and if they had missing clinical charts. Variables collected from charts included HIV diagnosis date, antiretroviral start date, baseline CD4+ T-cell count, baseline log viral load, development of adverse events and antiretroviral regimen change.

The primary outcome was the development of peripheral neuropathy related to d4T. Charts were retrospectively reviewed for signs and symptoms of new onset peripheral neuropathy and were graded for severity from grades 1 to 4 using the Division of AIDS Table for Grading Adult and Pediatric Adverse Events (version 1.0). Grade 1, or mild peripheral neuropathy, was defined as minimal sensory alteration/paraesthesia causing little interference with usual functional or social activities. Grade 2, or moderate peripheral neuropathy, was defined as sensory alteration/paraesthesia causing greater than minimal interference with usual functional or social activities. Grade 3, or severe peripheral neuropathy, was defined as sensory alteration/paraesthesia causing inability to perform usual social or functional activities. Grade 4 was defined as disabling sensory alteration/paraesthesia causing inability to perform basic self-care functions [12].

Data analysis was conducted using SAS version 9.1.3 (SAS Institute, Inc., Cary, NC, USA). Time to peripheral neuropathy was analysed with the use of Kaplan–Meier curves and the log-rank test. Duration in the study was calculated as the time from antiretroviral start to the first episode of peripheral neuropathy, withdrawal from study or at 24 months of follow-up, whichever occurred first. Poisson approximations were used to calculate CIs for the incidence rate of peripheral neuropathy. Proportional hazards regression models were used to adjust for potential confounding variables in the multivariate analysis. Fisher’s exact test was used for the analysis of categorical data, and unpaired t-tests or Wilcoxon two-sample test for the analysis of continuous data. In total, 298 patients were required in each cohort to detect a 10% difference in incidence of peripheral neuropathy between the 30 mg cohort and the 40 mg cohort with 80% power and an α-level of 0.5.
Peripheral neuropathy and stavudine

The study was approved by the University of KwaZulu-Natal’s Biomedical Research Ethics Committee and the Weill Cornell Medical College Institutional Review Board.

Results

Of the 602 patients selected, 127 were excluded. Patients were excluded if they had any treatment with antiretrovirals prior to enrolment into the study (n=3). Patients were also excluded if they had a history of peripheral neuropathy (n=79), if they had <6 months treatment follow-up (n=17) and if they had missing clinical charts (n=28). A total of 475 patients were analysed; 235 in the 40 mg cohort (cohort 1) with 152.7 person-years (py) of follow-up and 244.7 py of follow-up (Figure 1). A total of 48 patients in cohort 1 were initially started on 30 mg of d4T and dose escalated to 40 mg when their weight met the WHO criteria for dose escalation; 18.7 of the total py in cohort 1 were spent on 30 mg prior to the dose-escalation. The baseline characteristics of these patients are summarized in Table 1. There were no significant differences between the cohorts in age, sex, history of tuberculosis treatment, nadir CD4+ T-cell count and log viral load at baseline. There was a significant difference between the two cohorts in patients with concurrent tuberculosis, with more cases in the 30 mg cohort. The mean weight of subjects was also significantly greater in the 40 mg cohort.

Incidence of peripheral neuropathy was 90.4/100 py (95% CI 75.9, 106.8) in the 40 mg cohort versus 40.5/100 py (95% CI 32.9, 49.3) in the 30 mg group (incidence rate ratio 0.45; P<0.0001). In patients who were started on 40 mg and reduced to 30 mg after the mandated dose reduction, the incidence of peripheral neuropathy was 45.2/100 py (95% CI 21, 54) and was not statistically different from patients initiated on 30 mg alone (incidence rate ratio 0.89; P=0.62). As seen in Figure 2, there was a statistically significant difference between time to developing peripheral neuropathy in the two cohorts (P<0.0001).

There was no difference in the proportion of severe peripheral neuropathy cases (grade 3/4) between the two cohorts: 8.3% in the 40 mg group and 8.9% in the 30 mg group (P=1.0). As shown in Figure 3, there was no difference in time to developing severe peripheral neuropathy between the two cohorts (P=0.22).

Table 1. Baseline characteristics of study participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cohort 1: d4T 40 mg (n=235)</th>
<th>Cohort 2: d4T 30 mg (n=240)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (±sd)</td>
<td>34 (8.3)</td>
<td>33 (9.0)</td>
<td>0.20</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>169 (71.5)</td>
<td>163 (67.2)</td>
<td>0.40</td>
</tr>
<tr>
<td>Median nadir CD4+ T-cell count, cells/ml (range)</td>
<td>120 (2–391)</td>
<td>135 (2–648)</td>
<td>0.39</td>
</tr>
<tr>
<td>Median log HIV-1 viral load, copies/ml (range)</td>
<td>5.1 (2.6–6.6)</td>
<td>5.1 (1.6–6.9)</td>
<td>0.12</td>
</tr>
<tr>
<td>Mean bodyweight, kg (±sd)</td>
<td>66.2 (10.5)</td>
<td>56.4 (10.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bodyweight range, kg</td>
<td>42–111</td>
<td>31–84</td>
<td>–</td>
</tr>
<tr>
<td>Mean BMI, kg/m² (range)</td>
<td>24.8 (14.5–49.3)</td>
<td>22.8 (12.6–42.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of TB treatment, n (%)</td>
<td>47 (20.4)</td>
<td>64 (26.6)</td>
<td>0.13</td>
</tr>
<tr>
<td>Current TB treatment, n (%)</td>
<td>42 (18.3)</td>
<td>95 (39.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Highest grade of PN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1, n</td>
<td>60</td>
<td>20</td>
<td>–</td>
</tr>
<tr>
<td>Grade 2, n</td>
<td>82</td>
<td>72</td>
<td>–</td>
</tr>
<tr>
<td>Grade 3, n</td>
<td>8</td>
<td>8</td>
<td>–</td>
</tr>
<tr>
<td>Grade 4, n</td>
<td>6</td>
<td>1</td>
<td>–</td>
</tr>
</tbody>
</table>

BMI, body mass index; d4T, stavudine; PN, peripheral neuropathy; TB, tuberculosis.

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Figure 2. Kaplan-Meier failure plot of time to peripheral neuropathy

![Kaplan-Meier failure plot of time to peripheral neuropathy](image)

**Figure 3.** Kaplan-Meier failure plot of time to severe peripheral neuropathy

![Kaplan-Meier failure plot of time to severe peripheral neuropathy](image)

d4T, stavudine.
In univariate analyses (Table 2), increasing age (hazard ratio [HR] 1.78, 95% CI 1.35, 2.35) and d4T dose (HR 2.0, 95% CI 1.58, 2.61, with 30 mg dose as reference group) were the only significant predictors of the development of peripheral neuropathy. In a multivariate analysis (Table 2), an increased risk of developing peripheral neuropathy was associated with increasing age (HR 1.65, 95% CI 1.24, 2.19), d4T dose (HR 2.1, 95% CI 1.61, 2.74) and concurrent tuberculosis therapy (HR 1.41, 95% CI 1.06, 1.87). However, baseline CD4+ T-cell count, sex and weight were not associated with an increased risk of developing peripheral neuropathy. In univariate analysis, concurrent tuberculosis was not related to an increased risk of developing peripheral neuropathy; however, in multivariate analysis concurrent tuberculosis was associated with an increased risk. This could be explained by the interaction between concurrent tuberculosis and d4T dose (P<0.0001). We fitted a multivariate model including the interaction term, and similar results were obtained (data not shown). History of tuberculosis treatment prior to enrolment was not associated with an increased risk of developing peripheral neuropathy. Over the study duration pyridoxine was routinely given in conjunction with isoniazid. A separate multivariate model was constructed that included log baseline viral load, which was available on 330 patients. The other covariates were not qualitatively different when the multivariate model was fitted with viral load (data not shown).

**Table 2. Univariate and multivariate analysis of risk factors for development of peripheral neuropathy**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate model (Hazard ratio [95% CI])</th>
<th>P-value</th>
<th>Multivariate model (Hazard ratio [95% CI])</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (reference ≥40)</td>
<td>1.78 (1.35, 2.35)</td>
<td>&lt;0.0001</td>
<td>1.65 (1.24 to 2.19)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.27 (0.96, 1.67)</td>
<td>0.10</td>
<td>1.23 (0.92, 1.65)</td>
<td>0.16</td>
</tr>
<tr>
<td>Baseline CD4+ T-cell count</td>
<td>0.48</td>
<td></td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>≤50 cells/ml</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>51–100 cells/ml</td>
<td>1.24 (0.85, 1.82)</td>
<td></td>
<td>1.22 (0.82, 1.81)</td>
<td></td>
</tr>
<tr>
<td>101–150 cells/ml</td>
<td>1.23 (0.86, 1.74)</td>
<td></td>
<td>1.27 (0.88, 1.82)</td>
<td></td>
</tr>
<tr>
<td>151–200 cells/ml</td>
<td>0.93 (0.63, 1.39)</td>
<td></td>
<td>1.02 (0.68, 1.54)</td>
<td></td>
</tr>
<tr>
<td>&gt;200 cells/ml</td>
<td>1.22 (0.83, 1.80)</td>
<td></td>
<td>1.38 (0.92, 2.07)</td>
<td></td>
</tr>
<tr>
<td>d4T dose 40 mg versus 30 mg</td>
<td>2.03 (1.58, 2.61)</td>
<td>&lt;0.0001</td>
<td>2.10 (1.61, 2.74)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Past TB treatment</td>
<td>0.88 (0.65, 1.18)</td>
<td>0.39</td>
<td>0.91 (0.67, 1.25)</td>
<td>0.57</td>
</tr>
<tr>
<td>Current TB treatment</td>
<td>1.12 (0.86, 1.47)</td>
<td>0.39</td>
<td>1.41 (1.06, 1.87)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.86 (0.46, 7.47)</td>
<td>0.38</td>
<td>1.24 (0.88, 1.82)</td>
<td>0.77</td>
</tr>
<tr>
<td>Bodyweight, kg</td>
<td>1.02 (1.01, 1.03)</td>
<td>0.003</td>
<td>1.0 (0.99, 1.02)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

*Hazard ratios were obtained using proportional hazards regression. d4T, stavudine; TB, tuberculosis.*

Discussion

In this retrospective cohort study in a rural clinic in South Africa, we found that use of a lower dose of d4T was associated with a lower incidence of peripheral neuropathy. Incidence of peripheral neuropathy in the 40 mg cohort was extremely high and, although the incidence was lower in the reduced-dose cohort, the rate was nonetheless also high.

There was no difference in the proportion of severe peripheral neuropathy between the two cohorts. Symptoms of peripheral neuropathy can often be chronic in patients with severe peripheral neuropathy, despite discontinuation of d4T. The development of severe peripheral neuropathy, despite decreased dose, highlights the need for early discontinuation of d4T in patients who are maintained on d4T despite WHO recommendations.

In South Africa, a recent study looking at peripheral neuropathy in d4T-exposed patients after the dose reduction showed similar results. Of the 395 patients enrolled with ≥6 months exposure to d4T, 57% had symptomatic peripheral neuropathy and it was frequently associated with moderate to severe pain in the feet [13]. Like other studies, our findings show that older age is independently associated with the development of peripheral neuropathy. A similar study in South Africa looking at peripheral neuropathy risk factors in all patients with HIV found that 49% (n=598) of their study population was diagnosed with peripheral neuropathy and 30% of the study population had symptomatic peripheral neuropathy. In this study, d4T use was significantly associated with the development of peripheral neuropathy, as was older age and history of previous tuberculosis infection [14].

It is well known that the development of peripheral neuropathy affects quality of life and often symptom management is inadequate. Amitriptyline is often the only medication available for severe peripheral neuropathy in resource-limited settings. Despite the frequent use of amitriptyline it has not been found to be highly efficacious in clinical trials for the treatment of peripheral neuropathy [15].

Other studies in resource-limited settings have shown that the development of peripheral neuropathy is a
predictor of other toxicities, including severe hyperlactataemia [16]. The SWITCH study looked at a cohort of 3,333 HIV-infected adults on cART and found the most frequent reason for switching medications was toxicity and, among the individual antiretrovirals, d4T had a significantly higher switch score than other drugs [17]. In India, one study found that 13% of 183 patients receiving a regimen containing d4T stopped therapy secondary to peripheral neuropathy [18]. Similarly a recent study in Rwanda found that, among a cohort of 2,190 adults, 175 patients replaced d4T secondary to toxicity and specifically 8.0% for neuropathy [19]. Options for alternative antiretrovirals are scarce in resource-limited settings and this poses a grave threat to patients who require life-long treatment.

Due to the retrospective nature of this study, there are several limitations that are important to note. Patients were not randomized to the two doses of d4T, and temporal trends in patient management could have affected the results. The physical exam and patient interview were not standardized between different clinicians. There was limited data available on potential confounders including history or development of diabetes mellitus, history or current alcohol abuse, and other metabolic abnormalities, including vitamin B12 deficiency, that can contribute to the development of peripheral neuropathy. Diabetes was only included if the diagnosis was reported by the clinician in the chart and everyone else was considered non-diabetic by default. The study is also limited because the projected sample size was not met. Due to the short duration (June 2004–April 2006) that the patients were enrolled on d4T 40 mg prior to the guideline change, there were only a limited number of patients (n=300) who could be enrolled in the study. After applying exclusion criteria, 233 patients in cohort 1 and 240 patients in cohort 2 were included in the analysis. There was a significant difference between the two cohorts in patients with concurrent tuberculosis with more cases in the 30 mg cohort. It is possible that increased access to smear testing and tuberculosis treatment facilities after 2007 contributed to a case finding bias that led to this difference.

There have been few studies in resource-limited settings looking at the incidence of d4T-related peripheral neuropathy and specifically the effect of dose reduction on incidence and severity. Despite dose reduction, patients are at high risk of developing debilitating peripheral neuropathy and, in many cases, this neuropathy is irreversible if the offending drug is not discontinued in a timely manner. This study brings to light the importance of complying with WHO guidelines and providing acceptable alternatives to d4T, despite high cost. In countries where guidelines have not changed, patients are at risk for debilitating, often irreversible, side-effects and efforts should be made to change country-specific guidelines.

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Human experimentation guidelines of the US Department of Health and Human Services and those of the authors’ institutions were followed in the conduct of this research.

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Disclosure statement

The authors declare no competing interests.

References


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