Modification of the Incidence of Drug-Associated Symmetrical Peripheral Neuropathy by Host and Disease Factors in the HIV Outpatient Study Cohort

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Background. We sought to identify factors associated with the clinical diagnosis of symmetrical peripheral neuropathy (SPN) during the era of highly active antiretroviral therapy (HAART) in a retrospective, longitudinal cohort analysis.

Methods. Patients infected with human immunodeficiency virus type 1 were evaluated for clinical signs of SPN and its association with immunologic, virologic, clinical, and drug treatment factors by means of univariate and multivariate logistic regression analyses.

Results. Of 2515 patients, 329 (13.1%) received a diagnosis of SPN. In the logistic regression analysis, statistically significant non–drug-based risk factors for SPN were age >40 years (adjusted odds ratio [aOR], 1.17), diabetes mellitus (aOR, 1.79), white race (aOR, 1.33), nadir $CD4^+$ T lymphocyte count <50 cells/mm^3 (aOR, 1.64), $CD4^+$ T lymphocyte count 50–199 cells/mm^3 (aOR, 1.40), and viral load >10,000 copies/mL at first measurement (aOR, 1.44). Although initial use of didanosine, stavudine (40 mg b.i.d.), nevirapine, or 4 protease inhibitors was associated with SPN (ORs for all 4 treatments, >1.41), the strength of association decreased with continued use of all medications studied.

Conclusion. Since HAART was introduced, the incidence of SPN has decreased. Host factors and signs of increased disease severity were associated with an increased risk of developing SPN during the initial period of exposure to drug therapy. Immunity improved and the risk of SPN decreased with continued use of HAART. Delaying the initiation of therapy may select those individuals who will be more likely to develop SPN, and earlier initiation of HAART may decrease the risk of developing this common problem, as well as increase the therapeutic effects and decrease the toxic effects of the drugs.

Before the introduction of antiretroviral therapy, symmetrical peripheral neuropathy (SPN) was noted to be both common and increasingly prevalent over time in HIV-1–infected persons [1, 2]. HIV-associated SPN has a gradual onset and a slow progression [3], and many studies have shown an association of SPN with more advanced HIV-1 disease [4, 5].

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Certain nucleoside analogues have also been associated with the development of SPN. Compared with other types of peripheral neuropathy, SPN appears to have a more rapid onset [4, 6], and the pain is more severe [7, 8]. A number of hypotheses about the etiology of SPN have been proposed, including macrophage infiltration proximal to nerve endings due to preexisting damage from nutritional deficiencies and substance abuse [9–11], defects in the blood-nerve barrier in HIV-1–infected individuals, [12–15], and mitochondrial toxicity [16, 17]. Because we previously found an association between past severity of HIV-1 infection (namely, nadir [i.e., lowest ever] $CD4^+$ T lymphocyte count <200 cells/mm^3 [18, 19]) and lipoatrophy, and because there have been far fewer studies of SPN during the HAART era (compared with the pre-HAART era), we elected to study SPN and analyze the

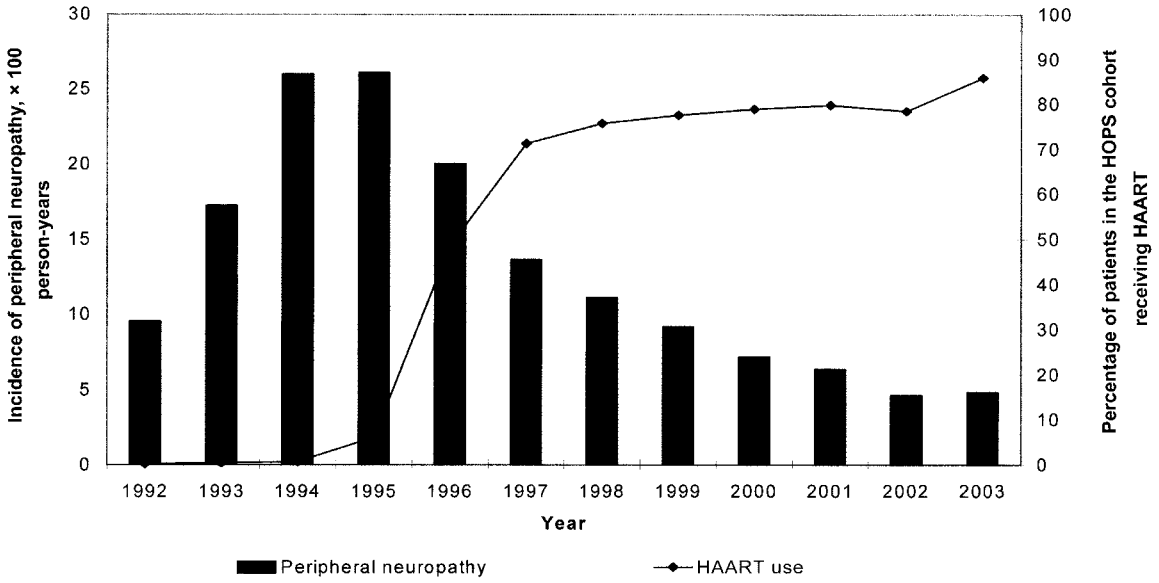

Figure 1. Incidence of peripheral neuropathy and rate of HAART use among 7362 patients in the HIV Outpatient Study (HOPS) cohort

association of various host, disease, and drug factors in a manner similar to that in our earlier study.

PATIENTS, MATERIALS, AND METHODS

HIV Outpatient Study (HOPS). HOPS has been described elsewhere [20]. This dynamic cohort includes HIV-1–infected persons seen at 9 clinics (2 private, 5 university affiliated, and 2 public) in 7 US cities (Chicago, IL; Denver, CO; Oakland, CA; Philadelphia, PA; Stony Brook, NY; Tampa, FL; and Washington, DC). HOPS-participating physicians routinely care for hundreds of HIV-1–infected patients and have extensive experience treating HIV-1 disease. Data from ongoing physician-patient interactions are electronically collected using the Clinical Practice Analyst data entry tool (Cerner Corporation) and are submitted for central processing and analysis. Such data include demographic characteristics, symptoms, diseases, treatments, and laboratory values. More than 7300 HIV-1–infected ambulatory patients have been seen during >201,000 outpatient visits to clinicians since 1992. The present analysis includes patient information collected prospectively from the time of entry into the study through 31 December 2003, as well as historical data based on documented records.

This ongoing study has been reviewed and approved annually by the Centers for Disease Control and Prevention (CDC; Atlanta, GA), Cerner Corporation (Vienna, VA), and local institutional review boards since its inception. Informed consent is obtained on an annual basis from all patients participating in HOPS. The informed consent documents are reviewed annually by the institutional review board of the CDC and by review boards at each of the participating sites. The study protocol conforms to the guidelines of the US Department of Health and Human Services.

SPN cohort and analysis. We identified patients in the HOPS cohort who received a clinical diagnosis of SPN that included the following chart entries: "peripheral neuropathy: due to treatment"; "peripheral neuropathy: due to HIV infection"; "peripheral neuropathy: other/unknown cause"; and "pain, tingling, or numbness in hands and/or feet." Because the clinical diagnosis of peripheral neuropathy is not always accurate, we limited our analysis to those patients whose sensory symptoms were distal and symmetrical. Patients with radiculopathy, proximal, or asymmetric symptoms were noted in the analysis as not having SPN. With the exception of data summarized in figures 1 and 2, we limited our analysis to patients in the HOPS cohort who were seen ⩾2 times through 31 December 2003, who had at least 1 $CD4^+$ T lymphocyte measurement and at least 1 viral burden test, and who had reliable data about the date of antiretroviral initiation. Figures 1 and 2 show our analysis of the incidence of peripheral neuropathy over time. Figure 1 summarizes data for the entire HOPS cohort of 7362 patients, and figure 2 summarizes data for 4397 patients in the HOPS cohort who were actively participating or were deceased.

Nadir $CD4^+$ T lymphocyte counts for the cohort were obtained, with a prediagnostic nadir $CD4^+$ T lymphocyte count recorded for patients who received a diagnosis of SPN. Antiretroviral history for each patient was reviewed to determine if any of the following medications had ever been used: the nucleoside analogues didanosine, stavudine, zidovudine, lamivudine, abacavir, and tenofovir; the protease inhibitors in-

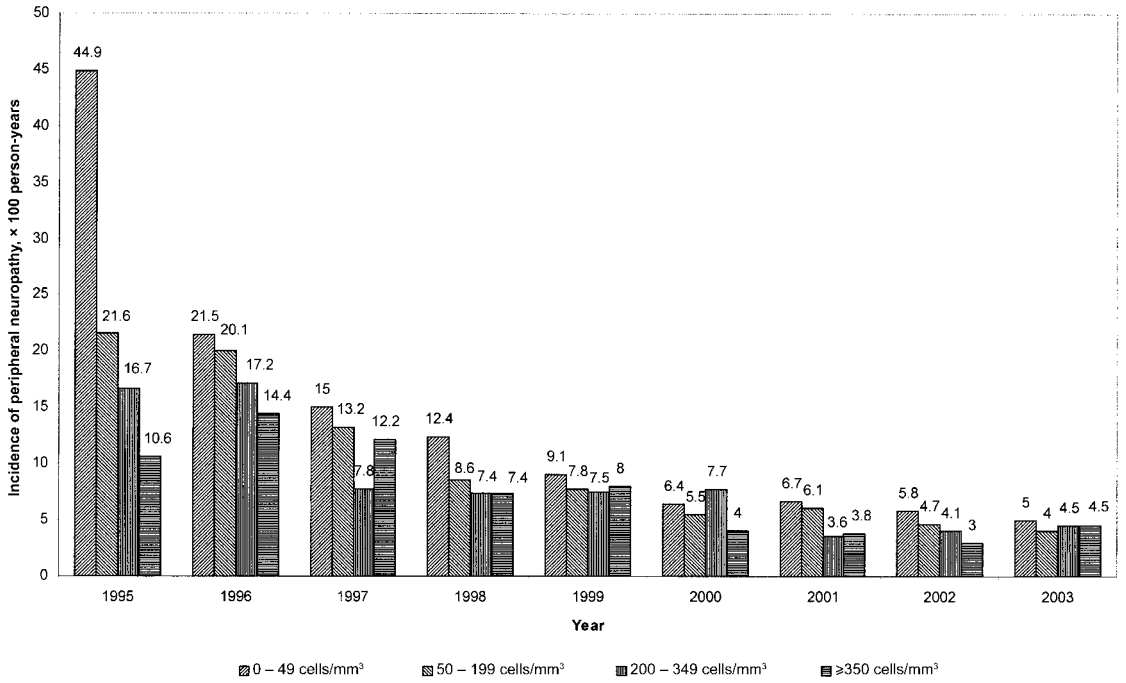

Figure 2. Incidence of peripheral neuropathy among 4397 patients (i.e., those who were actively participating in the cohort or were deceased) in the HIV Outpatient Study cohort, according to nadir CD4⁺ T lymphocyte count.

dinavir, ritonavir, saquinavir, nelfinavir, amprenavir, and lopinavir/ritonavir; and the nonnucleoside reverse transcriptase inhibitors (NNRTIs) nevirapine and efavirenz. Patients who had never taken antiretroviral therapy or who had not received antiretroviral drugs before the SPN diagnosis were also included in this study. Patient history before use of any HAART regimen was analyzed separately from patient history during antiretroviral use as part of a HAART regimen.

In the univariate analysis, host factors (age, race/ethnicity, sex, mode of HIV transmission, body mass index, presence of diabetes mellitus, and use of alcohol), immunologic factors (nadir CD4⁺ T lymphocyte count), virologic factors (results of the first viral burden test and of the most recent viral burden test before or at the time of SPN diagnosis), and any use of each antiretroviral drug were evaluated for their association with SPN.

For the logistic regression analyses, dose and duration of treatment with each individual nucleoside analogue, protease inhibitor, or NNRTI were transformed into binary variables whose values were based on duration of use (table 1). Host, immunologic, and virologic factors were included in the logistic regression analysis for each antiretroviral drug, as were interactions between all factors. A nomogram was created (table 2) on the basis of treatment durations of only those drugs that were associated with significant ORs, and these ratios were multiplied together to determine the composite OR for developing SPN for each HAART regimen.

Statistical analysis. Univariate analyses were performed using Statcalc, version 6 (EpiInfo 2002 revision 2; Centers for Disease Control and Prevention). Logistic regression analyses were performed with SAS software, version 8.2 (SAS Institute).

RESULTS

The incidence of patients with a clinical diagnosis of peripheral neuropathy increased during 1992–1995. However, starting with the introduction of HAART in 1996, the incidence of peripheral neuropathy has been progressively decreasing as the percentage of patients receiving HAART has increased (figure 1). Lower nadir CD4⁺ T lymphocyte counts were associated with higher rates of peripheral neuropathy, irrespective of the decrease in the use (beginning in 2000) of agents commonly associated with SPN (figure 2).

In the logistic regression analysis of SPN in the pre-HAART population, the following host and immunologic factors were significantly associated with incident SPN: no antiretroviral use, nadir CD4⁺ T lymphocyte count <200 cells/mm³, and white race. Up to 1 year of use of the following antiretroviral medications was associated with incident peripheral neuropathy: didanosine, "higher-dose" stavudine (40 mg b.i.d.), or zalcitabine. However, there was no association between the incidence of SPN and increasing duration of any drug treatment. After 1995, the host, immunologic, and disease factors significantly associated with incident SPN in the univariate analyses

were age >40 years at the time of the nadir $CD4^+$ T lymphocyte count, diabetes mellitus, nadir $CD4^+$ T lymphocyte count <50 cells/mm^3, and viral load >10,000 HIV RNA copies/mL at the time of the first viral burden test.

The host factors significantly associated with incident SPN in the logistic regression analysis after 1995 included age >40 years at the time of the nadir $CD4^+$ T lymphocyte count and diabetes mellitus (table 1). Nadir $CD4^+$ T lymphocyte count <50 cells/mm^3, nadir $CD4^+$ T lymphocyte count 50–199 cells/mm^3, and viral load >10,000 HIV RNA copies/mL at the time of the first measurement were the most significant immunologic and disease factors associated with SPN (table 1). On the basis of the -2 log–likelihood criterion, first viral load measurement created a more robust model than did peak viral load, and a viral load >10,000 copies/mL at the time of the first measurement created a more robust model than did the log of the first viral load measurement. Drugs that were independently associated with development of SPN in the first year of use included didanosine, higher-dose stavudine, indinavir, ritonavir, nelfinavir, saquinavir, and nevirapine (table 1). However, for patients who did not develop SPN in the first year of HAART, these drugs (except for HAART regimens containing both efavirenz and higher-dose stavudine) became negatively associated with development of SPN after 1 year of use (table 2). Any use of tenofovir was negatively associated with the development of SPN (table 1). When comparing HAART regimens that contained higher-dose stavudine with those that contained "lower-dose" stavudine ($\leqslant$30 mg b.i.d.), there were no differences in treatment responses with respect to $CD4^+$ T lymphocyte counts or viral loads. None of the interactions between host, immunologic, virologic, and treatment factors were statistically significant.

When stratifying by either nadir $CD4^+$ T lymphocyte count or the first viral load measurement, the percentage of patients developing SPN was highest among those with the lowest $CD4^+$ T lymphocyte counts or the highest viral burdens and progressively decreased among those with higher cell counts or lower viral burdens (figure 3). The analysis of drug-associated risk factors was performed on the basis of the cumulative duration of drug therapy, because in the stratified analysis, we found that, with each successive year of drug use, the risk of developing SPN progressively decreased among subjects who had no history of SPN (table 1).

By strength of association, individuals with multiple risk factors had an increased chance of developing SPN. To assess the risk of developing SPN, we developed a nomogram that took into account host and disease factors and the duration of the most commonly used HAART regimens (as defined by the 23 March 2004 US Department of Health and Human Services Guidelines for Use of Antiretroviral Agents in HIV-1–Infected Adults and Adolescents) (table 2). For the preferred HAART regimens shown in table 2 (and for several other regimens not displayed), risk was highest during the first year in which such regimens were used and was even higher among patients with lower nadir $CD4^+$ cell counts, higher viral loads at the time of the first ever measurement, increasing age, and diabetes mellitus (table 2). Regimens containing higher-dose stavudine had the greatest likelihood of being associated with SPN during the first year of use, compared with regimens containing efavirenz, tenofovir, or lopinavir/ritonavir, which were less likely to be associated with SPN during this period. However, if SPN did not develop after 1 year of use, all regimens (except those involving treatment with higher-dose stavudine, lamivudine, and efavirenz) were associated with negative risk of developing SPN (OR, <1.0) (table 2).

DISCUSSION

Our study is the largest cohort-based analysis of SPN since the introduction of HAART. We found that the incidence and prevalence of SPN increased during the pre-HAART era after the introduction of nucleoside analogue therapy and that the prevalence of SPN among antiretroviral-naive patients in our cohort was 14.7%. Although consistent with results in other cohort studies that demonstrated an increased prevalence of SPN as the duration of HAART increased [1, 2, 21], we also found that, since 1997, the incidence of SPN has been progressively decreasing. If SPN did not develop within the first year of use of any antiretroviral agent, it was less likely to occur in subsequent years. In fact, the risk of SPN decreased as the percentage of patients exposed to any drug or combination of drugs increased. We recognized that SPN can be caused by HIV disease, as well as by the drugs used to treat HIV disease. However, in this study, among patients for whom onset of SPN was associated with use of particular antiretroviral drugs, the disease factors still persisted as independently associated risk factors. The analysis of risk factors for SPN found that the combined indices of disease severity—namely, nadir $CD4^+$ cell count and plasma HIV RNA load at the time of the first measurement—were a nearly equivalent or stronger predictor of developing SPN than was any type of antiretroviral drug used, with the exception of higher-dose stavudine.

Our study is consistent with most other studies of HIV-associated peripheral neuropathy with regard to prevalence, incidence, association with markers of advanced HIV-1 disease, and use of various antiretroviral agents [1, 2, 4, 6]. We also found associations between SPN and age, diabetes mellitus, white race, markers of disease severity, and several nucleoside analogues and protease inhibitors. As with previous studies, we found that, if SPN was going to occur, it did so within months and certainly within the first year after initial exposure to the antiretroviral agent [1, 2, 6].

Table 1. Factors for symmetrical peripheral neuropathy (SPN) in 2515 patients in the HIV Outpatient Study.

Factor	Received diagnosis of SPN, no. (%) of patients		Univariate analysis		Logistic regression analysis[a]	
	Yes (n = 329)	No (n = 2186)	OR (95% CI)	P	Adjusted OR (95% CI)	P
Age >40 years at time of nadir $CD4^+$ cell count[b]	162 (49.2)	916 (41.9)	1.35 (1.07–1.72)	.012	1.17 (1.02–1.33)	.022
White race	196 (59.6)	1187 (54.3)	1.24 (0.97–1.58)	.083	1.33 (1.05–1.70)	.020
Diabetes mellitus	26 (7.9)	101 (4.6)	1.77 (1.10–2.83)	.016	1.79 (1.12–2.84)	.014
Nadir $CD4^+$ cell count <50 cells/mm^3	87 (26.4)	416 (19.0)	1.53 (1.16–2.01)	.002	1.64 (1.21–2.22)	.002
Nadir $CD4^+$ cell count 50–199 cells/mm^3	99 (30.1)	560 (25.6)	1.25 (0.96–1.62)	.098	1.40 (1.06–1.86)	.018
First HIV RNA load >10,000 copies/mL	211 (64.1)	1160 (53.1)	1.58 (1.24–2.03)	<.001	1.44 (1.12–1.85)	.005
ART received before onset of SPN, duration in years						
Didanosine	112 (34.0)	574 (26.3)	1.45 (1.12–1.87)	.004		
>0 to <1	…	…	…		2.20 (1.63–2.98)	<.001
1 to <2	…	…	…		0.89 (0.53–1.49)	.659
2 to <3	…	…	…		0.80 (0.38–1.69)	.562
⩾3	…	…	…		0.55 (0.27–1.10)	.092
Stavudine (40 mg b.i.d.)	164 (49.8)	813 (37.2)	1.68 (1.32–2.13)	<.001		
>0 to <1	…	…	…		3.32 (2.49–4.43)	<.001
1 to <2	…	…	…		2.06 (1.40–3.04)	<.001
2 to <3	…	…	…		0.65 (0.33–1.27)	.205
⩾3	…	…	…		0.35 (0.19–0.64)	<.001
Stavudine (⩽30 mg b.i.d.)	37 (11.2)	324 (14.8)	0.73 (0.50–1.06)	.101		
>0 to <1	…	…	…		1.18 (0.74–1.88)	.485
⩾1	…	…	…		0.38 (0.21–0.68)	.001
Zidovudine	116 (35.3)	1092 (50.0)	0.55 (0.43–0.70)	<.001		
>0 to <1	…	…	…		0.82 (0.61–1.12)	.210
1 to <2	…	…	…		0.43 (0.27–0.70)	<.001
2 to <3	…	…	…		0.47 (0.27–0.83)	.009
⩾3	…	…	…		0.24 (0.14–0.41)	<.001
Epivir	202 (61.4)	1611 (73.7)	0.55 (0.44–0.73)	<.001		
>0 to <1	…	…	…		1.13 (0.84–1.52)	.421
1 to <2	…	…	…		0.59 (0.41–0.86)	.005
2 to <3	…	…	…		0.40 (0.26–0.63)	<.001
⩾3	…	…	…		0.18 (0.12–0.28)	<.001
Abacavir	46 (14.0)	461 (21.1)	0.61 (0.43–0.85)	<.003		
>0 to <1	…	…	…		0.84 (0.55–1.27)	.399
1 to <2	…	…	…		0.50 (0.25–0.99)	.048
⩾2	…	…	…		0.35 (0.18–0.69)	.003
Tenofovir	14 (3.2)	357 (14.3)	0.23 (0.13–0.40)	<.001		
>0 to <1	…	…	…		0.27 (0.14–0.51)	<.001
⩾1	…	…	…		0.15 (0.06–0.42)	<.001
Indinavir	144 (43.8)	764 (34.9)	1.45 (1.14–1.84)	<.002		
>0 to <1	…	…	…		2.13 (1.58–2.86)	<.001
1 to <2	…	…	…		1.40 (0.92–2.12)	.115
2 to <3	…	…	…		0.92 (0.51–1.66)	.792
⩾3	…	…	…		0.38 (0.22–0.67)	<.001
Ritonavir (⩾800 mg/day)	68 (20.7)	295 (13.5)	1.67 (1.23–2.26)	<.001		
>0 to <1	…	…	…		2.10 (1.49–2.96)	<.001
1 to <2	…	…	…		0.89 (0.42–1.91)	.772
2 to <3	…	…	…		0.70 (0.21–2.33)	.561
⩾3	…	…	…		0.26 (0.06–1.10)	.067
Nelfinavir	121 (36.8)	768 (35.1)	1.07 (0.84–1.38)	.603		
>0 to <1	…	…	…		1.61 (1.19–2.17)	.002
1 to <2	…	…	…		1.03 (0.67–1.58)	.895
2 to <3	…	…	…		0.56 (0.28–1.14)	.109
⩾3	…	…	…		0.33 (0.17–0.65)	.001

(continued)

Table 1. ***(Continued.)***

Factor	Received diagnosis of SPN, no. (%) of patients		Univariate analysis		Logistic regression analysis[a]	
	Yes (n = 329)	No (n = 2186)	OR (95% CI)	P	Adjusted OR (95% CI)	P
Saquinavir	83 (25.2)	376 (17.2)	1.62 (1.23–2.15)	<.001		
>0 to <1	…	…	…		1.93 (1.38–2.70)	<.001
1 to <2	…	…	…		1.39 (0.82–2.36)	.226
2 to <3	…	…	…		0.83 (0.32–2.13)	.692
⩾3	…	…	…		0.46 (0.16–1.29)	.139
Lopinavir/ritonavir	30 (9.1)	292 (13.4)	0.65 (0.43–0.98)	.040		
>0 to <1	…	…	…		0.95 (0.61–1.49)	.834
1 to <2	…	…	…		0.23 (0.07–0.75)	.014
⩾2	…	…	…		0.15 (0.04–0.63)	.009
Nevirapine	88 (26.7)	649 (29.7)	0.86 (0.66–1.13)	.304		
>0 to <1	…	…	…		1.41 (1.04–1.91)	.025
1 to <2	…	…	…		0.56 (0.30–1.03)	.063
2 to <3	…	…	…		0.17 (0.04–0.71)	.015
⩾3	…	…	…		0.38 (0.18–0.83)	.015
Efavirenz	86 (26.1)	740 (33.9)	0.69 (0.53–0.91)	.007		
>0 to <1	…	…	…		1.00 (0.73–1.38)	.990
1 to <2	…	…	…		0.71 (0.44–1.14)	.151
2 to <3	…	…	…		0.26 (0.10–0.64)	.004
⩾3	…	…	…		0.20 (0.08–0.50)	<.001

NOTE. ART, antiretroviral therapy; RTI, reverse-transcriptase inhibitor.

[a] Multivariate analysis adjusted for age, race, diabetes mellitus, nadir $CD4^+$ cell count, and first measured viral load.

[b] Modeled as a continuous variable in the logistic regression analysis.

Yet, there are also important differences and findings between this study and many that have preceded it. Although some studies have been published since the introduction of HAART [22–24], most research in this field was done in earlier years (i.e., before 1996) and may not have taken into account HAART-based improvement in patients with HIV-1 disease. As the effectiveness of suppression of HIV-1 disease with HAART has improved, the associations of various factors with SPN have changed.

The association of peripheral neuropathy with markers of HIV disease severity is well described [1, 3–5, 14, 22, 25]. Our study suggests that the association of markers of advanced disease with SPN may occur as a result of an as-yet-undefined pathophysiologic mechanism induced by an advanced state of illness, as has been reported elsewhere [26]. This finding suggests that individuals who develop SPN are predisposed to it because of injury to nerve tissue [9, 10].

Several hypotheses have been advanced to explain why peripheral neuropathy is more likely to occur with advancing HIV disease. One hypothesis proposes that nutritional deficiencies, alcohol or other toxic substances, or HIV infection itself may cause axonal injury that attracts hyperactivated macrophages [1, 3–5, 9, 10, 14]. The cytokines elaborated by these cells are more toxic to the nerves [12, 13]. Another study suggests that this macrophage and cytokine contact may be due to a faulty blood-nerve barrier in patients with HIV-1 infection [23]. Additionally, there is evidence of an association between HIV-1 replication in dorsal root ganglia and macrophage infiltration of perineural spaces [12, 13, 27]. Several studies also postulate mitochondrial toxicity as a cause of SPN [16, 17], whereas others question this hypothesis [28–31]. Finally, the dideoxynucleosides (didanosine, zalcitabine, and stavudine) have been shown to be neurotoxic [6, 32].

A finding in our study that differs from that in most other studies is the strong association of SPN with protease inhibitor use. Although this finding could represent colinearity, we did not see it with zidovudine, lamivudine, or NNRTIs, all of which also were frequently used by patients in our cohort. Perhaps the protease inhibitors act synergistically with some of the nucleoside analogues by increasing intracellular concentrations of nucleoside analogues, either directly or indirectly, in individuals who are more susceptible to peripheral neuropathy owing to preexisting nerve injury.

However, as our study shows, use of any of these antiretroviral agents will, over time, lead to decreased risk of SPN in treated patients. We think this may indicate some other or additional mechanisms to those outlined above. In fact, Anderson and colleagues [33] have shown that the intracellular concentration of triphosphorylated nucleoside analogues is higher in individuals with lower $CD4^+$ T lymphocyte counts. As the $CD4^+$ T lymphocyte count increases in response to therapy, the intracellular concentration of the nucleoside analogues decreases. Elsewhere, Anderson and colleagues [34] postulated that more advanced HIV disease increases the state of cellular

Table 2. Nomogram of composite ORs (likelihoods) for developing symmetrical peripheral neuropathy with most commonly used HAART regimens, according to immunologic and virologic status.

HAART regimen, duration in years	Composite OR, according to nadir $CD4^+$ cell count and plasma HIV RNA load				
	<50 cells/mm^3 and >10^4 copies/mL	50–199 cells/mm^3 and >10^4 copies/mL	<50 cells/mm^3 and <10^4 copies/mL	50–199 cells/mm^3 and <10^4 copies/mL	⩾200 cells/mm^3 and <10^4 copies/mL
ZDV/3TC/LPVr					
<1	2.36	2.02	1.64	1.40	1.00
1 to <2	0.14	0.12	0.10	0.08	0.06
2 to <3	0.07	0.06	0.05	0.04	0.03
⩾3	0.02	0.01	0.01	0.01	< 0.01
D4T (40 mg b.i.d.)/3TC/LPVr					
<1	7.84	6.71	5.44	4.65	3.32
1 to <2	0.66	0.57	0.46	0.39	0.28
2 to <3	0.14	0.12	0.10	0.08	0.06
⩾3	0.02	0.02	0.02	0.01	0.01
D4T (⩽30 mg b.i.d.)/3TC/LPVr					
<1	2.36	2.02	1.66	1.42	1.00
1 to <2	0.12	0.11	0.09	0.07	0.05
2 to <3	0.05	0.05	0.04	0.03	0.02
⩾3	0.02	0.02	0.02	0.01	0.01
TDF/3TC/LPVr					
<1	0.64	0.55	0.44	0.38	0.27
1 to <2	0.05	0.04	0.03	0.03	0.02
2 to <3	0.02	0.02	0.01	0.01	0.01
⩾3	0.01	0.01	<0.01	<0.01	<0.01
ZDV/3TC/EFV					
<1	2.36	2.02	1.64	1.40	1.00
1 to <2	0.60	0.51	0.42	0.36	0.26
2 to <3	0.12	0.10	0.08	0.07	0.05
⩾3	0.02	0.02	0.01	0.01	0.01
D4T (40 mg b.i.d.)/3TC/EFV					
<1	7.84	6.71	5.44	4.65	3.32
1 to <2	2.88	2.46	2.00	1.71	1.22
2 to <3	0.25	0.21	0.17	0.15	0.10
⩾3	0.03	0.03	0.02	0.02	0.01
D4T (⩽30 mg b.i.d.)/3TC/EFV					
<1	2.36	2.02	1.64	1.40	1.00
1 to <2	0.53	0.45	0.37	0.32	0.22
2 to <3	0.09	0.08	0.07	0.06	0.04
⩾3	0.03	0.03	0.02	0.02	0.01
TDF/3TC/EFV					
<1	0.64	0.55	0.44	0.38	0.27
1 to <2	0.21	0.18	0.15	0.12	0.09
2 to <3	0.04	0.03	0.03	0.02	0.02
⩾3	0.01	0.01	0.01	0.01	< 0.01

NOTE. D4T, stavudine; EFV, efavirenz; LPVr, lopinavir/ritonavir; TDF, tenofovir; ZDV, zidovudine; 3TC, lamivudine. ORs can be adjusted according to age as follows: age 20–24 years, multiply by 0.79; age 25–29 years, by 0.82; age 30–34 years, by 0.89; age 35–39 years, by 0.96; age 40–44 years, by 1.03; age 45–49 years, by 1.11; age 50–54 years, by 1.20; age 55–59 years, by 1.30; age 60–64 years, by 1.40; and age ⩾65 years, by 1.51. ORs can be adjusted for diabetes mellitus by multiplying by 1.79.

activation. This, in turn, is hypothesized to increase nucleoside analog phosphorylation, resulting in higher intracellular concentrations of drug.

In animal studies, researchers have been unable to induce peripheral neuropathy or other dideoxynucleoside-related toxicities in rats or primates with high doses of these drugs in the absence of HIV infection [35]. Such findings suggest that preexisting nerve injury predisposes individuals infected with HIV-1 to SPN by virtue of exposure to proinflammatory cytokines (TNF-α, IL-6, and IFN-γ) mediated by hyperactivated macrophages. Biopsy and autopsy studies have demonstrated pathologic findings in nerves in individuals with advanced HIV-1

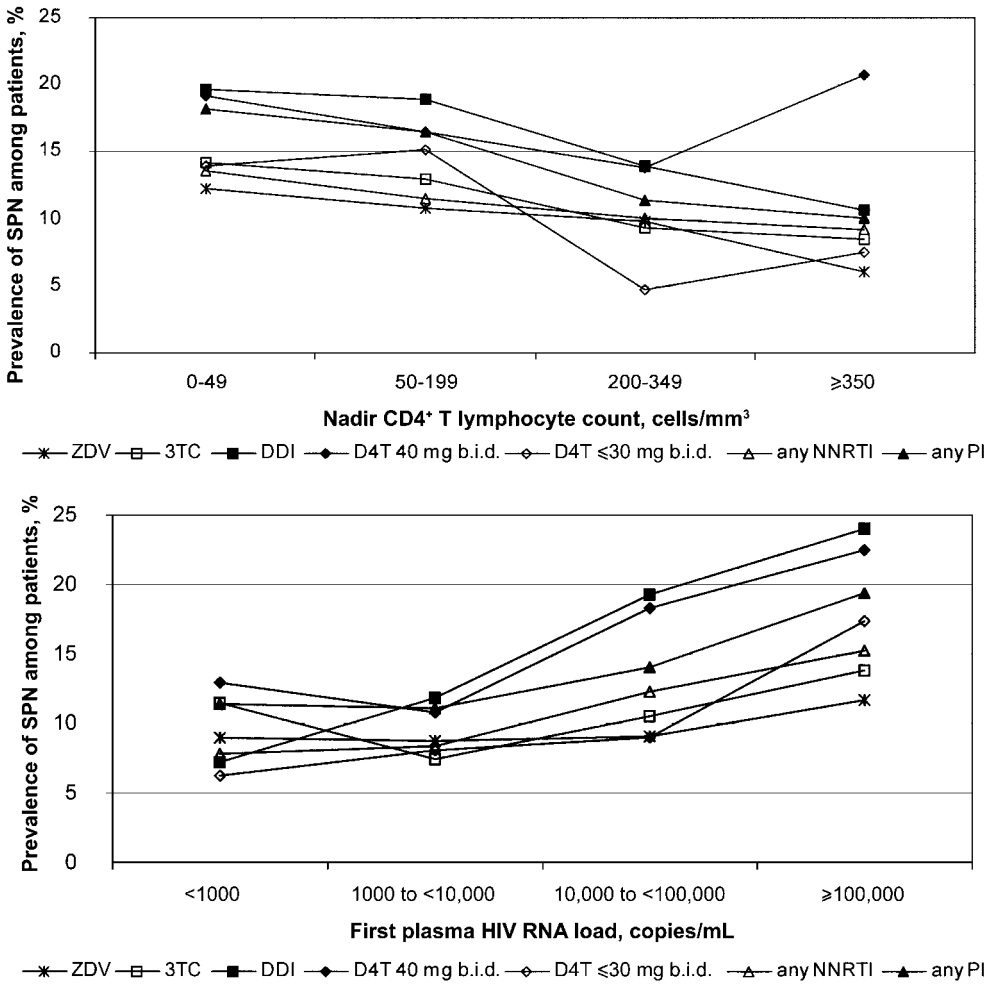

Figure 3. Prevalence of symmetrical peripheral neuropathy (SPN) among 2515 patients in the HIV Outpatient Study cohort who were receiving various commonly administered HAART regimens, according to nadir $CD4^+$ cell count *(A)* and first viral load measurement *(B)*. DDI, didanosine; D4T, stavudine; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; ZDV, zidovudine; 3TC, lamivudine.

infection who did not have clinical SPN [3]. It has been proposed that, in advanced disease, some clones of T lymphocytes—notably those that produce IL-10 and IL-4 cytokines that oppose macrophage activation—may be permanently destroyed or substantially diminished [14, 15]. During the initial response to treatment, there may be only partial repletion of the cellular repertoire, resulting in production of unopposed proinflammatory cytokines that are directly toxic to nerve cells or neurons or that increase nucleoside analogue phosphorylation. Individuals with less severe disease progression may maintain more control over cytokine regulation, and consequently, be at lower risk of developing SPN.

This study has several limitations. Patients in this study were determined to have SPN on the basis of extraction of clinical diagnoses from medical charts; such diagnoses are not always accurate without supportive studies or evaluations performed by neurologists [36]. Studies of nerve conduction, measurements of temperature and other sensory parameters, and nerve biopsies could not be performed because of the retrospective nature of this analysis. However, HIV clinicians are necessarily limited in their use of these tests and almost always rely on a clinical diagnosis of peripheral neuropathy. Recognizing these limitations, we limited our analysis only to those patients with peripheral, distal, and symmetrical manifestations. This cohort was likely comprised mostly of patients with distal symmetrical polyneuropathy. Yet, subjects with other diagnoses were possibly included because of the lack of confirmatory clinical findings and test results. Nevertheless, the purpose of this analysis was to generate hypotheses to help researchers design studies to understand the pathophysiology of SPN and guide subsequent clinical decisions for this common comorbidity.

Our data is necessarily left-censored. We do not have complete records of $CD4^+$ T lymphocyte counts and viral burdens for all patients. Because such data were absent for some patients, it is likely that the absence would bias our study against finding an association between SPN and lower nadir $CD4^+$ T lympho-

cyte counts or higher viral burdens. We did not assess adherence to the various drug regimens. We did evaluate treatment interruptions in the cohort and found that they were more frequent among patients with more advanced disease. However, only very large systematic biases in adherence would change our findings, which were quite consistent from drug to drug.

This epidemiological analysis suggests that disease progression and host factors strongly predispose individuals to the neurotoxic effects of antiretroviral medications. It suggests that delaying the initiation of therapy may actually select individuals who will be more likely to develop SPN and that earlier initiation of HAART may result in a significantly lower risk of developing this common problem and thus widen the ratio of therapeutic to toxic effects of the drugs.

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References

1. So YT, Holtzman DM, Abrams DI, Olney RK. Peripheral neuropathy associated with acquired immunodeficiency syndrome: prevalence and clinical features from a population-based survey. Arch Neurol **1988**; 45:945–8.
2. Schifitto G, McDermott MP, McArthur JC, et al. Incidence of and risk factors for HIV-associated distal sensory polyneuropathy. Neurology **2002**; 58:1764–8.
3. Tagliati M, Grinnell J, Godbold J, Simpson DM. Peripheral nerve function in HIV infection: clinical, electrophysiologic, and laboratory findings. Arch Neurol **1999**; 56:84–9.
4. Bacellar H, Munoz A, Miller EN, et al. Temporal trends in the incidence of HIV-1–related neurologic diseases: multicenter AIDS Cohort Study, 1985–1992. Neurology **1994**; 44:1892–900.
5. Childs EA, Lyles RH, Selnes OA, et al. Plasma viral load and CD4 lymphocytes predict HIV-associated dementia and sensory neuropathy. Neurology **1999**; 52:607–13.
6. Blum AS, Dal Pan GJ, Feinberg J, et al. Low-dose zalcitabine–related toxic neuropathy: frequency, natural history, and risk factors. Neurology **1996**; 46:999–1003.
7. Oh SB, Tran PB, Gillard SE, Hurley RW, Hammond DL, Miller RJ. Chemokines and glycoprotein 120 produce pain hypersensitivity by directly exciting primary nociceptive neurons. J Neurosci **2001**; 21: 5027–35.
8. Herzberg U, Sagen J. Peripheral nerve exposure to HIV viral envelope protein gp120 induces neuropathic pain and spinal gliosis. J Neuroimmunol **2001**; 116:29–39.
9. Berger AR, Schaumburg HH, Gourevitch MN, Freeman K, Herskovitz S, Arezzo JC. Prevalence of peripheral neuropathy in injection drug users. Neurology **1999**; 53:592–7.
10. Moyle GJ, Sadler M. Peripheral neuropathy with nucleoside antiretrovirals: risk factors, incidence and management. Drug Saf **1998**; 19: 481–94.
11. Kieburtz KD, Giang DW, Schiffer RB, Vakil N. Abnormal vitamin B12 metabolism in human immunodeficiency virus infection: association with neurological dysfunction. Arch Neurol **1991**; 48:312–4.
12. Nagano I, Shapshak P, Yoshioka M, Xin K, Nakamura S, Bradley WG. Increased NADPH-diaphorase reactivity and cytokine expression in dorsal root ganglia in acquired immunodeficiency syndrome. J Neurol Sci **1996**; 136:117–28.
13. Yoshioka M, Shapshak P, Srivastava AK, et al. Expression of HIV-1 and interleukin-6 in lumbosacral dorsal root ganglia of patients with AIDS. Neurology **1994**; 44:1120–30 (erratum: Neurology 1994; 44:1504–5).
14. Tyor WR, Wesselingh SL, Griffin JW, McArthur JC, Griffin DE. Unifying hypothesis for the pathogenesis of HIV-associated dementia complex, vacuolar myelopathy, and sensory neuropathy. J Acquir Immune Defic Syndr **1995**; 9:379–88.
15. Oswald IP, Wynn TA, Sher A, James SL. Interleukin 10 inhibits macrophage microbicidal activity by blocking the endogenous production of tumor necrosis factor α required as a costimulatory factor for interferon γ–induced activation. Proc Natl Acad Sci U S A **1992**; 89: 8676–80.
16. Kakuda TN. Pharmacology of nucleoside and nucleotide reverse transcriptase inhibitor–induced mitochondrial toxicity. Clin Ther **2000**; 22: 685–708.
17. Dalakas MC, Semino-Mora C, Leon-Monzon M. Mitochondrial alterations with mitochondrial DNA depletion in the nerves of AIDS patients with peripheral neuropathy induced by 2′3′-dideoxycytidine (ddC). Lab Invest **2001**; 81:1537–44.
18. Lichtenstein KA, Ward DJ, Moorman AC, et al. Clinical assessment of HIV-associated lipodystrophy in an ambulatory population. AIDS **2001**; 15:1389–98.
19. Lichtenstein KA, Delaney KM, Armon C, et al. Incidence of and risk factors for lipoatrophy (abnormal fat loss) in ambulatory HIV-1–infected patients. J Acquir Immune Defic Syndr **2003**; 32:48–56.
20. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection [comment]. HIV Outpatient Study Investigators. N Engl J Med **1998**; 338:853–60.
21. Cherry C, Costello K, Woolley I, Mijch A, Wesselingh S. Increasing

prevalence of neuropathy in the era of highly active antiretroviral therapy (HAART) [abstract 69]. In: Program and abstracts of the Ninth Conference on Retroviruses and Opportunistic Infections (Seattle). Alexandria, VA: Foundation for Retrovirology and Human Health, **2002**:76.
22. Keswani SC, Pardo CA, Cherry CL, Hoke A, McArthur JC. HIV-associated sensory neuropathies [review]. AIDS **2002**; 16:2105–17.
23. Geraci AP, Simpson DM. Neurological manifestations of HIV-1 infection in the HAART era. Compr Ther **2001**; 27:232–41.
24. Simpson DM, Haidich AB, Schifitto G, et al. Severity of HIV-associated neuropathy is associated with plasma HIV-1 RNA levels. AIDS **2002**; 16:407–12.
25. Simpson DM, Tagliati M. Nucleoside analogue–associated peripheral neuropathy in human immunodeficiency virus infection. J Acquir Immune Defic Syndr Hum Retrovirol **1995**; 9:153–61.
26. Cornblath DR, McArthur JC. Predominantly sensory neuropathy in patients with AIDS and AIDS-related complex. Neurology **1988**; 38: 794–6.
27. Brannagan TH III, Nuovo GJ, Hays AP, Latov N. Human immunodeficiency virus infection of dorsal root ganglion neurons detected by polymerase chain reaction in situ hybridization. Ann Neurol **1997**; 42: 368–72.
28. Benbrik E, Chariot P, Bonavaud S, et al. Cellular and mitochondrial toxicity of zidovudine (AZT), didanosine (ddI) and zalcitabine (ddC) on cultured human muscle cells. J Neurol Sci **1997**; 149:19–25.
29. Chen CH, Vazquez-Padua M, Cheng YC. Effect of anti–human immunodeficiency virus nucleoside analogs on mitochondrial DNA and its implication for delayed toxicity. Mol Pharmacol **1991**; 39:625–8.
30. Cui L, Locatelli L, Xie MY, Sommadossi JP. Effect of nucleoside analogs on neurite regeneration and mitochondrial DNA synthesis in PC-12 cells. J Pharmacol Exp Ther **1997**; 280:1228–34.
31. Skuta G, Fischer GM, Janaky T, et al. Molecular mechanism of the short-term cardiotoxicity caused by 2′,3′-dideoxycytidine (ddC): modulation of reactive oxygen species levels and ADP-ribosylation reactions. Biochem Pharmacol **1999**; 58:1915–25.
32. Browne MJ, Mayer KH, Chafee SB, et al. 2′,3′-Didehydro-3′-deoxythymidine (d4T) in patients with AIDS or AIDS-related complex: a phase I trial. J Infect Dis **1993**; 167:21–9.
33. Anderson PL, Kakuda TN, Kawle S, Fletcher CV. Antiviral dynamics and sex differences of zidovudine and lamivudine triphosphate concentrations in HIV-infected individuals. AIDS **2003**; 17:2159–68.
34. Anderson PL, Kakuda TN, Lichtenstein KA. The cellular pharmacology of nucleoside- and nucleotide-analogue reverse-transcriptase inhibitors and its relationship to clinical toxicities. Clin Infect Dis **2004**; 38: 743–53.
35. Kaul S, Dandekar KA, Schilling BE, Barbhaiya RH. Toxicokinetics of 2′,3′-didehydro-3′-deoxythymidine, stavudine (D4T). Drug Metab Dispos **1999**; 27:1–12.
36. Simpson DM, Katzenstein DA, Hughes MD, et al. Neuromuscular function in HIV infection: analysis of a placebo-controlled combination antiretroviral trial. AIDS Clinical Group 175/801 Study Team. AIDS **1998**; 12:2425–32.