Incident Neuropathy in HIV-Infected Patients on HAART

Beau K. Nakamoto,^{1,2} Aaron McMurtry,¹ James Davis,¹ Victor Valcour,³ Michael R. Watters,¹
Bruce Shiramizu,¹ Dominic C. Chow,¹ Kalpana Kallianpur,¹ and Cecilia M. Shikuma¹

Abstract

We determined the incidence of and risk factors for distal sensory polyneuropathy (DSP) in individuals on HAART. Sixty-one HIV-positive subjects on HAART for at least 6 months and neuropathy free were retrospectively selected. The study included subjects who had previously tolerated d-drugs without developing DSP. Neuropathy incidence over 4 years was calculated. Cox proportional hazards models were used to determine risk factors associated with incident DSP. Nineteen subjects developed DSP over a mean follow-up of 2.4 years. Subjects never treated with a d-drug developed DSP at a rate of 21 cases per 100 person-years (95% CI, 8.9–33.7). Subjects with a history of d-drug treatment but not on a d-drug at enrollment developed DSP at a rate of 17 cases per 100 person-years (95% CI, 2.1–31.8). Those on d-drug treatment developed DSP at a rate of 25 cases per 100 person-years (95% CI, 8.7–41.6). Multivariable analysis identified age [hazard ratio (HR) = 1.09; $p < 0.01$] and low CD4⁺ nadir [hazard ratio (HR) = 0.79; $p = 0.03$] as significant risk factors. Current or prior history of treatment with d-drug was not a significant risk factor for incident DSP in subjects who had previously tolerated d-drug treatment without developing a toxic DSP. Age and low CD4⁺ are risk factors for incident DSP. However, current or prior history of d-drug treatment is not a significant risk factor for incident DSP in subjects who had previously tolerated d-drug treatment without developing a toxic DSP.

Introduction

SINCE THE INTRODUCTION OF HIGHLY ACTIVE antiviral therapy (HAART) in 1996, the spectrum of neurologic complications associated with HIV infection has changed. The incidence of immunodeficiency-associated central nervous system (CNS) disorders, such as toxoplasmosis, cryptococcal meningitis, primary CNS lymphoma, and progressive multifocal leukoencephalopathy, has decreased dramatically.¹ Nonetheless, HIV-associated distal sensory neuropathy (DSP) continues to be a common neurologic complication seen in HIV-seropositive individuals.^{2–4} Patients usually present with the gradual onset of distal sensory symptoms in the feet, including numbness, paresthesias, or painful dysesthesias.⁵ The painful dysesthesias can be severe enough to limit activities of daily living.⁶

Prior to the use of HAART, HIV-associated DSP was associated with markers of advanced immunosuppression (e.g., high plasma HIV viral load, reduced CD4⁺ lymphocyte cell count),⁷ affecting approximately one-third of infected patients.⁵ In the early HAART era, three dideoxynucleoside re-

verse transcriptase inhibitors (d-NRTI)—zalcitabine (Hivid, 2',3'-dideoxycytidine or ddC), stavudine (Zerit, 2',3'-didehydro-3'-deoxythymidine or d4T), didanosine (Videx, dideoxyinosine or ddi)—known collectively as “d-drugs” caused toxic DSP, which was clinically difficult to differentiate from HIV-associated DSP.^{8–11}

The risk of developing a toxic DSP from a d-drug usually peaks in the first 3 months of initiating therapy.¹² One study¹³ suggested that if DSP did not develop within the first year of using a d-drug, it was less likely to occur in subsequent years. Nonetheless, it is still controversial whether exposure to d-drugs has a cumulative toxic effect and whether continued d-drug exposure in those who had previously tolerated these agents without neurotoxicity is associated with an increased risk of developing DSP. D-drugs were extensively used in the United States and Europe, and the issue of continued future risk associated with previous d-drug use is of particular relevance as the HIV-infected population ages. Moreover, as medications with less neuropathy risk replace the use of d-drugs in resource-limited countries, it is important to determine whether

¹Hawaii Center for AIDS, Department of Medicine, John A. Burns School of Medicine, University of Hawaii, Honolulu, Hawaii.

²Department of Neurology, Straub Clinics and Hospital, Honolulu, Hawaii.

³Division of Geriatric Medicine and Memory and Aging Center, Department of Neurology, University of California San Francisco, San Francisco, California.

patients tolerating d-drugs necessarily need to switch to other HIV medications to avoid higher risk of neuropathy if they are doing well. This study therefore aimed to determine the incidence of and risk factors for DSP in patients on HAART with particular attention to assessing potential incident neuropathy risk in individuals who had previously tolerated treatment with a d-drug without developing DSP.

Materials and Methods

Study design

A retrospective convenience sample of subjects who were on HAART and without DSP at enrollment was selected from the Hawaii Aging with HIV Cohort (HAHC) (Fig. 1).

Hawaii aging with HIV cohort

The HAHC was a prospective study examining the relationship between aging and neurocognitive impairment in HIV-infected individuals. Details of enrollment and clinical characterization have been published elsewhere.¹⁴

Briefly, 141 older (≥ 50 years of age) and 125 younger (< 40 years of age) HIV-infected individuals residing in the state of Hawaii were enrolled from October 22, 2001 to July 1, 2005. Primary exclusion criteria included premorbid or comorbid conditions that might limit completion or interpretation of neuropsychiatric evaluations, including intravenous drug use, within 6 months of enrollment, active major psychiatric disorders, history of traumatic brain injury with loss of consciousness for more than 1 h, poorly controlled epilepsy, history of stroke, active CNS opportunistic disease, and learning

disabilities. Baseline and annual evaluations included demographic data, medical and medication history, a neurologic examination, and HIV laboratory parameters (plasma HIV viral load, current CD4⁺ lymphocyte cell count, and self-reported lowest ever CD4⁺ lymphocyte cell count). All subjects signed informed consent, and the institutional review board at the University of Hawaii approved the study.

Neuropathy assessment

The HAHC study utilized a macroneurological examination for the assessment of neuropathy created by the AIDS Clinical Trials Group.¹⁵ The examination included tests of sensation to pinprick, light touch, and vibration on all four extremities, comparing proximal (at or above the knee/elbow) to distal sensation (at or below the ankle/great toe/wrist/finger). Vibratory impairment was defined as less than 10 s of perception after a 128-Hz tuning fork was struck with maximal force and applied to the base of the great toe, ankle, knee, distal interphalangeal joint of the middle finger, or wrist. A semiquantitative assessment of severity based on level of neuropathic signs was performed. Sensation to each modality was documented as no impairment, impairment at or below the ankles/wrists, impairment between the ankle and knees/wrist and elbow, or impairment at or above the knees/elbows. Ankle reflexes were examined and compared to deep tendon reflexes at the knee. Diagnosis of a DSP required both diminished or absent ankle jerks reflexes compared to the knee and a diminution of sensation in at least one modality present in the lower extremities bilaterally. Symptomatic DSP required an examination consistent with DSP

FIG. 1. Flow chart of subject selection and outcome.

and the presence of two or more neuropathic symptoms, which included numbness, tingling, burning, stinging, hypersensitivity, or pain. Electrophysiologic studies, autonomic reflex tests, and skin biopsies were not performed.

Statistical analysis

Statistical analysis was performed with SAS 9.1 (Cary, NC). Means, standard deviations, and proportions were calculated for baseline characteristics. Incidence of DSP in 100 person-years was defined as the number of incident cases of neuropathy divided by the total duration of at-risk and multiplied by 100. A Cox proportional hazards model was used to test the null hypothesis that rate of progression to DSP is no different between subjects never treated with a d-drug, subjects currently on d-drug treatment, and subjects with a history of treatment with a d-drug but not on a d-drug at study enrollment. The presence or absence of DSP on neurological examination was the dependent variable. Based on the results of previous published studies,^{5,16,17} age, CD4⁺ nadir, years of d-drug treatment, current HIV RNA viral load, and current CD4⁺ cell count were included as independent variables. Univariable analysis was performed, followed by a multivariable analysis that included independent variables with a *p*-value ≤ 0.1 in the univariable analysis.

Results

Subject characteristics

Sixty-one HIV-positive subjects without DSP and on HAART at enrollment were included in this analysis (Fig. 1). The demographics and clinical characteristics of these subjects are summarized in Table 1. Twenty-six subjects (43%) were never treated with d-drugs. Fifteen subjects (24%) had a history of treatment with a d-drug but were not on a d-drug at study enrollment. Twenty subjects (33%) were on d-drug treatment at enrollment. A majority of the subjects had un-

detectable HIV viral loads and CD4⁺ cell counts greater than 200 cells/ μ l. A minority of the subjects had current alcohol abuse defined by the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)*,¹⁸ neurotoxic drug exposure other than a d-drug (e.g., isoniazid, hydroxyurea, ethambutol), or other neurotoxic medical comorbidities (e.g., diabetes, impaired glucose tolerance, uremia, vitamin B₁₂ deficiency, thyroid disorders, connective tissue disorders, syphilis, or solvent exposures).

The sample contained two groups: 28 older (≥50 years of age) and 33 younger (<40 years of age) subjects. The older group were HIV seropositive longer (13 years, standard deviation 5.7 years) compared to the younger group (8 years, standard deviation 6.0 years, *p* < 0.01). There were no statistically significant differences between the older and younger groups in CD4⁺ nadir, proportion who had any d-drug exposure (i.e., history of d-drug treatment but not on a d-drug at enrollment or on d-drug treatment at enrollment), and proportion who developed incident symptomatic DSP.

Neuropathy incidence

Nineteen subjects developed a DSP over a mean follow-up of 2.4 years (Fig. 1). Subjects with no history of d-drug treatment developed a DSP at a rate of 21 cases per 100 person-years (95% CI, 8.9–33.7 cases per 100 person-years). Subjects with a history of d-drug treatment but not on a d-drug at enrollment developed a DSP at a rate of 17 cases per 100 person-years (95% CI, 2.1–31.8 cases per 100 person-years), whereas those on d-drugs developed a DSP at a rate of 25 cases per 100 person-years (95% CI, 8.7–41.6 cases per 100 person-years).

Neuropathy risk factors

Univariable analysis identified age and CD4⁺ nadir as significant risk factors (Table 2). These risk factors were included

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF SUBJECTS

	n = 61
Mean age of all subjects, years (SD)	44.2 (10.2)
Mean age of younger subjects (<40 years of age)	35.7 (4.9)
Mean age of older subjects (≥50 years of age)	54.2 (3.0)
Males (%)	84
White (%)	51
Self-reported years HIV positive (SD)	10.4 (6.3)
With undetectable viral load, copies/ml (%)	69
With CD4 count >200, cells/ μ l (%)	92
Nadir CD4 count, cells/ μ l (SD)	424 (223)
Never treated with a d-drug (%)	43
With a history of treatment with a d-drug but NOT on a d-drug at study enrollment (%)	24
Currently on d-drug therapy at study enrollment (%)	33
With current alcohol abuse ^a (%)	8
With other neurotoxic drug exposure ^b (%)	8
With neurotoxic medical comorbidities ^c (%)	8
Years of follow-up (SD)	2.4 (1.1)

^aCurrent alcohol abuse was defined by *Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)*.¹⁸

^bOther neurotoxic drug exposures were obtained by self-report and included isoniazid, hydroxyurea, and ethambutol.

^cNeurotoxic medical comorbidities were obtained by self-report/medical chart review and included diabetes, impaired glucose tolerance, uremia, vitamin B₁₂ deficiency, thyroid disorders, connective tissue disorders, syphilis, and solvent exposure (e.g., carbon disulfide, *n*-hexane, methyl butyl ketone, perchloroethylene, trichloroethylene, toluene).

TABLE 2. UNIVARIATE ANALYSIS OF RISK FACTORS ASSOCIATED WITH THE RATE DEVELOPING A DISTAL SENSORY POLYNEUROPATHY

	Hazard ratio	p Value	95% confidence interval
Age (per year)	1.05	0.04	1.003–1.10
CD4 ⁺ nadir per 100 cells/ μ l	0.82	0.02	0.69–0.97
On d-drug at enrollment ^a	1.39	0.47	0.57–3.35
History of treatment with a d-drug but <i>not</i> on d-drug at enrollment ^a	0.63	0.44	0.19–2.05
Years HIV positive	1.04	0.34	0.96–1.11
Detectable viral load (>50 copies/ml)	1.88	0.14	0.80–4.39
CD4 ⁺ count <200 cells/ μ l	1.25	0.66	0.46–3.38
Alcohol abuse ^b	0.30	0.23	0.04–2.20
History of other neurotoxic drug exposure ^c	0.91	0.67	0.58–1.42
History of neurotoxic medical comorbidity ^d	1.38	0.60	0.41–4.68

^aSubjects never treated with a d-drug were used as the reference group.

^bCurrent alcohol abuse was defined as defined by *Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)*.¹⁸

^cOther neurotoxic drug exposures were obtained by self-report and included isoniazid, hydroxyurea, and ethambutol.

^dNeurotoxic medical comorbidities were obtained by self-report/medical chart review and included diabetes, impaired glucose tolerance, uremia, vitamin B₁₂ deficiency, thyroid disorders, connective tissue disorders, syphilis, and solvent exposure (e.g., carbon disulfide, *n*-hexane, methylbutyl-ketone, perchloroethylene, trichloroethylene, toluene).

in a multivariable analysis. A subject's d-drug exposure history was also included in the model since this was a variable of interest. Subjects currently on a d-drug and those with history of d-drug treatment but not on a d-drug at enrollment were compared to subjects never treated with a d-drug.

Multivariable analysis identified age and CD4⁺ nadir as significant risk factors associated with incident DSP (Table 3). The incidence of DSP increased by 9% for every year of age [hazard ratio (HR) = 1.09; $p < 0.01$] and increased by 21% for every 100 cells/ml decrease in CD4⁺ nadir [hazard ratio (HR) = 0.79; $p = 0.03$]. Using subjects never treated with a d-drug as the reference group, subjects currently on a d-drug and those with prior d-drug exposure but not on a d-drug at enrollment were not significant risk factors associated with incident DSP.

Length of exposure to d-drug

Fifteen subjects had a history of d-drug treatment but were not on a d-drug at enrollment (Fig. 1). These subjects had previously been treated with d-drugs for a median of 1.0 years (interquartile range of 0.60–4.41 years); three developed a DSP. Twenty subjects were on d-drug treatment at enrollment. These subjects were treated for a median of 3.7 years (interquartile range 3.0–5.3 years). Seven of these subjects developed a DSP; 57% (4/7) developed a DSP within the first year of follow-up. A higher percentage of subjects with

either a history of d-drug treatment but not on a d-drug at enrollment or currently on d-drug therapy developed a symptomatic DSP (9/35, 26%) compared to those who were never treated with a d-drug (2/26, 8%, Fig. 1). The difference, however, did not reach statistical significance ($p = 0.10$). The small number of outcomes prevented further analysis to look for trends based on years of exposure or type of d-drug.

Discussion

This study followed 61 HIV-positive subjects on HAART and without DSP at enrollment over 4 years for the development of DSP. Our study included subjects never treated with a d-drug and those who had tolerated d-drug treatment without developing a toxic DSP. Our finding suggests that incident DSP risk is not increased in subjects who currently or previously tolerated d-drugs without developing a toxic DSP.

Prior to HAART, HIV-associated DSP occurred in 35% of patients infected with HIV and was associated with advanced immunosuppression.⁵ The association of high plasma HIV viral load and reduced CD4⁺ lymphocyte cell count with HIV-associated DSP was consistent with this observation.⁷ In the HAART era, DSP continues to be a common neurologic complication of patients infected with HIV despite suppression of HIV viral loads and maintenance of higher CD4⁺ lymphocyte cell counts.¹ This continued prevalence of DSP may partially be secondary to residual HIV-induced effect on

TABLE 3. MULTIVARIATE ANALYSIS OF RISK FACTORS ASSOCIATED WITH THE RATE OF DEVELOPING A DISTAL SENSORY POLYNEUROPATHY

	Hazard ratio	p Value	95% confidence interval
Age (per year)	1.09	<0.01	1.02–1.15
CD4 ⁺ nadir per 100 cells/ μ l	0.79	0.03	0.64–0.97
On d-NRTI at enrollment ^a	1.79	0.27	0.64–5.04
History of treatment with a d-drug but NOT on d-NRTI at enrollment ^a	0.73	0.63	0.20–2.71

^aSubjects never treated with a d-drug were used as the reference group. d-NRTI, dideoxynucleoside reverse transcriptase inhibitor.

peripheral nerves perhaps mediated by proinflammatory cytokines (e.g., tumor necrosis factor- α , interleukin-1, interleukin-6) secreted by HIV-infected macrophages.¹⁹

In the HAART era, particular antiviral therapies, collectively known as "d-drugs," were found to cause a toxic DSP, occurring in up to 34% of patients.^{8–11} Classically, symptoms are usually temporally related to the start of therapy occurring in the first 6 weeks of exposure. Although symptomatic improvement can occur with very early drug cessation, there is usually incomplete resolution of symptoms and signs.¹⁹ It is currently believed that the toxic DSP related to d-drug therapy is the result of mitochondrial toxicity related to the inhibition of mitochondrial DNA polymerase-gamma.¹¹

It is well established that DSP continues to be a prevalent neurologic complication associated with HIV infection in the HAART era, occurring in 36–62% of subjects infected with HIV.^{1–4} Little is known about the incidence of DSP in the era of HAART. Lichtenstein *et al.*¹³ reported an incidence of five cases per 100 person-years from the HIV Outpatient Study (HOPS). However, they included only symptomatic DSP in their study, and our study's higher incidence rate may have resulted from our inclusion of both asymptomatic and symptomatic DSP cases. Our cohort was also enriched with older individuals. Our results do not contradict the higher rates of incident DSP (36–54%) reported in cohort studies from sub-Saharan Africa^{20,21} where d4T was used given that our sample included subjects who had already demonstrated an ability to tolerate these drugs without developing DSP.

In the HAART era, the risk factors associated with prevalent DSP in subjects infected with HIV have changed. High plasma HIV viral loads and decreased current CD4⁺ cell counts are no longer associated with DSP.^{2,22} A prior study from HAHC has identified age greater than 50 years and nadir CD4⁺ cell counts below 200 cells/ μ l as a risk factor associated with prevalent DSP.¹⁶ This has been confirmed in other studies.^{13,23,24}

Our study found that nadir CD4⁺ cell counts and age are also significant risk factors for incident DSP in the era of HAART (Tables 2 and 3). The relationship of nadir CD4⁺ cell counts with incident and prevalent cases of DSP is possibly the result of damage to the peripheral nervous system that occurred at a time when the plasma HIV viral load was higher and CD4⁺ cell counts were lower.¹³

Since the introduction of HAART in 1996, individuals infected with HIV are living longer and understanding the interaction between age and medical/drug-related comorbidities will become increasingly important. Cherry *et al.*²⁵ propose that the development of DSP could be the result of reduced neurologic reserve. In the aging HIV population, the peripheral nervous system will be affected by the inflammatory cascade from dysfunctional macrophages¹⁹ in addition to other medical comorbidities, such as alcohol abuse, diabetes, B₁₂ deficiency, and concurrent infection with hepatitis C virus. Mitochondrial dysfunction also occurs with increased age.²⁶ There have been concerns that older HIV-infected individuals treated with mitochondrial toxic d-drugs might decrease neurologic reserve, unmasking preexisting subclinical peripheral nerve damage due to HIV.^{27,28}

Symptomatic DSP is more common in older (≥ 50 years of age) HIV-infected individuals.¹⁶ There was no significant difference in proportion of symptomatic DSP in the younger

(<40 years of age) and older groups in our study, likely due to the small number of this outcome. Although symptomatic neuropathy was not the primary outcome of this study, there was a trend toward a higher incidence of symptomatic DSP in d-drug-experienced subjects (9/35, 26%) versus those never treated with a d-drug (Fig. 1). Given that d-drugs, especially d4T, are still used in resource-limited settings^{4,29,30} and some believe that the relationship between d-drugs and the development of symptomatic DSP results from the unmasking of preexisting subclinical peripheral nerve damage by the toxic agents, future studies to determine risk factors involved with the development of symptomatic DSP and progression of an asymptomatic to symptomatic DSP are warranted. Cherry *et al.*³⁰ and Affandi *et al.*²⁹ found that d4T neuropathy risk increases with age and height and suggest that prioritizing older and taller subjects to alternative antiviral therapies would be one inexpensive strategy to reduce DSP in resource-limited settings.

Our study did not find a significance difference in incidence of DSP between subjects never treated with a d-drug and those with a history of d-drug treatment. This can in part be explained by a selection bias. Subjects selected for this analysis were free of DSP at enrollment, and those with a history of d-drug exposure who had already developed a DSP were excluded. Therefore, this population was likely relatively resistant to d-drug toxicity, which may explain our findings (Tables 2 and 3). This is consistent with the finding from Lichtenstein *et al.*¹³ that if DSP does not develop within the first year of use of d-NRTI it is less likely to occur in subsequent years. A recent study by Hung *et al.*³¹ also found that subjects tolerating an initial trial of a d-drug did not have an increased risk of progression of neuropathic signs or symptoms compared to subjects not on a d-drug. Our finding adds to the literature by emphasizing that there is no ongoing residual increase in DSP risk for subjects who received and tolerated d-drugs in the past and that there appears to be no significant added DSP risk if d-drugs are continued in subjects currently tolerating d-drug. The former is important information for patients in developed countries many of whom received d-drugs in the past. The latter is important information for subjects in resource-limited countries in assessing the risk of continued d4T use. Although d-drugs have other toxicities such as lipoatrophy associated with their use,³² this information will assist physicians with treatment decisions in resource-limited settings where d-drugs remain one of the few affordable treatment options for individuals infected with HIV.

We recognize the limitations of the current study. First, there was a small number of outcomes in our study, and a type-II error may account for our finding that the risk of developing a toxic DSP may not increase with d-drug exposure. The small number of outcomes also prevented subgroup analysis between asymptomatic and symptomatic DSP. Second, DSP was a clinical diagnosis, and the incidence of DSP may have been underestimated since electrophysiologic studies or skin biopsies were not performed. Third, since asymptomatic and symptomatic DSP were the outcomes of interest, the reliability of the examination could be a concern. In the HAHC, however, neurologic examinations were performed by the same two investigators (V.V., M.R.W.). One was a neurologist and the second an internist with semianual quality assurance on the technique. Fourth, subjects were

not systematically evaluated for B₁₂ deficiency or hepatitis C virus status, and we were unable to determine the contribution of these confounders to the risk of incident DSP. Fifth, the reason for the discontinuation of the d-drug was not collected, and this could account for the decreased incidence associated with subjects who had a history of d-drug treatment but were not on a d-drug at enrollment.

In summary, our findings show that current or prior use of d-drugs is not a significant risk factor for incident DSP in subjects who had previously tolerated d-drug treatment without developing a toxic DSP. Age and nadir CD4⁺ count appear to be important risk factors for incident DSP. Perhaps future studies should address whether initiating antiviral therapy earlier or tailoring therapy based on age may minimize incident DSP risk.

Acknowledgments

This study was supported by research Grants R01NS063932 NINDS/NIH "HIV and Global Drug Therapies: Peripheral Neuropathy Complications and Mechanisms," P200RR011091 NCRR/NIH Clinical Research Center, U54 NS4 NINDS/NIH NeuroAIDS Specialized Neuroscience Research Program, R25 RR019321 Clinical Research Education and Career Development (CRECD) in Minority Institutions "Master in Biomedical Science Program in Clinical Research," K07 GM072884 Curriculum Development Award in Interdisciplinary Research "PhD in Biomedical Science Program in Clinical Research." Thank you to Roseanne Harrigan, Ed.D. and the members of the Master and Ph.D. in Biomedical Science Program in Clinical Research for reviewing this chapter. Statistical analysis was performed by James Davis, Ph.D., John A. Burns School of Medicine, University of Hawaii, Honolulu, HI.

Author Disclosure Statement

Dr. Valcour is a consultant for Merck and Glaxo Smith Kline. Dr. Shikuma receives research/training funding support from Pfizer, Merck, and Gilead Pharmaceuticals, and has served on an advisory board for Glaxo Smith Kline.

References

1. Sacktor N, Lyles RH, Skolasky R, *et al.*: HIV-associated neurologic disease incidence changes: Multicenter AIDS Cohort Study, 1990–1998. *Neurology* 2001;56(2):257–260.
2. Morgello S, Estanislao L, Simpson D, *et al.*: HIV-associated distal sensory polyneuropathy in the era of highly active antiretroviral therapy: The Manhattan HIV Brain Bank. *Arch Neurol* 2004;61(4):546–551.
3. Skopelitis EE, Kokotis PI, Kontos AN, *et al.*: Distal sensory polyneuropathy in HIV-positive patients in the HAART era: An entity underestimated by clinical examination. *Int J STD AIDS* 2006;17(7):467–472.
4. Smyth K, Affandi JS, McArthur JC, *et al.*: Prevalence of and risk factors for HIV-associated neuropathy in Melbourne, Australia 1993–2006. *HIV Med* 2007;8(6):367–373.
5. So YT, Holtzman DM, Abrams DI, and Olney RK: Peripheral neuropathy associated with acquired immunodeficiency syndrome. Prevalence and clinical features from a population-based survey. *Arch Neurol* 1988;45(9):945–948.
6. Pandya R, Krentz HB, Gill MJ, and Power C: HIV-related neurological syndromes reduce health-related quality of life. *Can J Neurol Sci* 2005;32(2):201–204.
7. Childs EA, Lyles RH, Selnes OA, *et al.*: Plasma viral load and CD4 lymphocytes predict HIV-associated dementia and sensory neuropathy. *Neurology* 1999;52(3):607–613.
8. Berger AR, Arezzo JC, Schaumburg HH, *et al.*: 2',3'-Dideoxycytidine (ddC) toxic neuropathy: A study of 52 patients. *Neurology* 1993;43(2):358–362.
9. Blum AS, Dal Pan GJ, Feinberg J, *et al.*: Low-dose zalcitabine-related toxic neuropathy: Frequency, natural history, and risk factors. *Neurology* 1996;46(4):999–1003.
10. Kiebertz KD, Seidlin M, Lambert JS, Dolin R, Reichman R, and Valentine F: Extended follow-up of peripheral neuropathy in patients with AIDS and AIDS-related complex treated with dideoxyinosine. *J Acquir Immune Defic Syndr* 1992;5(1):60–64.
11. Simpson DM and Tagliati M: Nucleoside analogue-associated peripheral neuropathy in human immunodeficiency virus infection. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995;9(2):153–161.
12. Arenas-Pinto A, Bhaskaran K, Dunn D, and Weller IV: The risk of developing peripheral neuropathy induced by nucleoside reverse transcriptase inhibitors decreases over time: Evidence from the Delta trial. *Antivir Ther* 2008;13(2):289–295.
13. Lichtenstein KA, Armon C, Baron A, Moorman AC, Wood KC, and Holmberg SD: Modification of the incidence of drug-associated symmetrical peripheral neuropathy by host and disease factors in the HIV outpatient study cohort. *Clin Infect Dis* 2005;40(1):148–157.
14. Valcour V, Shikuma C, Shiramizu B, *et al.*: Higher frequency of dementia in older HIV-1 individuals: The Hawaii Aging with HIV-1 Cohort. *Neurology* 2004;63(5):822–827.
15. Division of AIDS table for grading severity of adult adverse experiences. National Institute of Allergy and Infectious Disease, Rockville, MD, 2004.
16. Watters MR, Poff PW, Shiramizu BT, *et al.*: Symptomatic distal sensory polyneuropathy in HIV after age 50. *Neurology* 2004;62(8):1378–1383.
17. Tagliati M, Grinnell J, Godbold J, and Simpson DM: Peripheral nerve function in HIV infection: Clinical, electrophysiologic, and laboratory findings. *Arch Neurol* 1999;56(1):84–89.
18. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. American Psychiatric Association, Washington, DC, 2000.
19. Gonzalez-Duarte A, Robinson-Papp J, and Simpson DM: Diagnosis and management of HIV-associated neuropathy. *Neurol Clin* 2008;26(3):821–832.
20. Forna F, Liechty CA, Solberg P, *et al.*: Clinical toxicity of highly active antiretroviral therapy in a home-based AIDS care program in rural Uganda. *J Acquir Immune Defic Syndr* 2007;44(4):456–462.
21. Sacktor N, Nakasujja N, Skolasky RL, *et al.*: Benefits and risks of stavudine therapy for HIV-associated neurologic complications in Uganda. *Neurology* 2009;72(2):165–170.
22. Simpson DM, Kitch D, Evans SR, *et al.*: HIV neuropathy natural history cohort study: Assessment measures and risk factors. *Neurology* 2006;66(11):1679–1687.
23. Valcour V, Yee P, Williams AE, *et al.*: Lowest ever CD4 lymphocyte count (CD4 nadir) as a predictor of current cognitive and neurological status in human immunodeficiency virus type 1 infection—The Hawaii Aging with HIV Cohort. *J Neurovirol* 2006;12(5):387–391.

24. Cherry CL, Skolasky RL, Lal L, *et al.*: Antiretroviral use and other risks for HIV-associated neuropathies in an international cohort. *Neurology* 2006;66(6):867–873.
25. Cherry CL, McArthur JC, Hoy JF, and Wesselingh SL: Nucleoside analogues and neuropathy in the era of HAART. *J Clin Virol* 2003;26(2):195–207.
26. Yen WL and Klionsky DJ: How to live long and prosper: Autophagy, mitochondria, and aging. *Physiology (Bethesda)* 2008;23:248–262.
27. Mallal SA, John M, Moore CB, James IR, and McKinnon EJ: Contribution of nucleoside analogue reverse transcriptase inhibitors to subcutaneous fat wasting in patients with HIV infection. *AIDS* 2000;14(10):1309–1316.
28. Delta: A randomised double-blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV-infected individuals. Delta Coordinating Committee. *Lancet* 1996;348(9023):283–291.
29. Affandi JS, Price P, Imran D, Yuniastuti E, Djauzi S, and Cherry CL: Can we predict neuropathy risk before stavudine prescription in a resource-limited setting? *AIDS Res Hum Retroviruses* 2008;24(10):1281–1284.
30. Cherry CL, Affandi JS, Imran D, *et al.*: Age and height predict neuropathy risk in patients with HIV prescribed stavudine. *Neurology* 2009;73(4):315–320.
31. Hung CF, Gibson SA, Letendre SL, *et al.*: Impact of long-term treatment with neurotoxic dideoxynucleoside antiretrovirals: Implications for clinical care in resource-limited settings. *HIV Med* 2008;9(9):731–737.
32. Shikuma CM, Gerschenson M, Chow D, *et al.*: Mitochondrial oxidative phosphorylation protein levels in peripheral blood mononuclear cells correlate with levels in subcutaneous adipose tissue within samples differing by HIV and lipodystrophy status. *AIDS Res Hum Retroviruses* 2008;24(10):1255–1262.

Address correspondence to:

Beau Nakamoto
Straub Clinics and Hospital
888 South King Street
Honolulu, Hawaii 96813

E-mail: beau_nakamoto@yahoo.com