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Frequency and Characteristics of HIV-Associated Sensory Neuropathy Among HIV Patients in Bangkok, Thailand

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To the Editor:

HIV-associated sensory neuropathy (HSN) encompasses distal sensory polyneuropathy and antiretroviral toxic neuropathy with clinical features between the two that are indistinguishable.¹ In the absence of antiretroviral (ARV) medications, HSN is as frequent as 30% among patients with AIDS.² Immunosuppression and higher plasma HIV RNA levels increase both risk and severity.³ Dideoxynucleoside reverse transcription inhibitors (dNRTIs) add additional risk that may induce or unmask underlying neuropathy.⁴ Although less frequently employed in developed countries, dNRTIs, particularly stavudine (d4T), are commonly used in developing countries due to low cost. Here, HSN rates after initiation of predominantly d4T-containing ARV therapy range from 6% to 20.7%, with one Thai study reporting 6.9% after 48 weeks of treatment.^{5–8}

We present a cross-sectional study of HSN from an outpatient infectious diseases (ID) clinic at Phramongkutklao Medical Center in Bangkok, Thailand. Approved by the Phramongkutklao Medical Center Institutional Review Board, this study screened 118 cases and enrolled 100 subjects between January and July 2006 by approaching all outpatients attending the clinic in consecutive order on days when the neurology staff was available (approximately 2 days of each month). Subjects had to be 14 years and above with documented HIV. Exclusion criteria were inability to sign consent or the presence of confounding factors known to potentially influence neuropathy (eg, neurotoxic chemotherapeutic treatment, diabetes, alcoholism, and chronic renal failure). History of HIV, comorbid illnesses, opportunistic infections, illicit drug use, and medication profiles including ARV history were obtained from chart review and participant interview. When available within 3 months before entry, CD4 lymphocyte counts (85/100) and plasma HIV RNA (37/100) were recorded.

The neurological evaluation utilized standardized methodology as applied in the AIDS Clinical Trials Group (ACTG) noting proximity of distal sensory impairments in pinprick, temperature, vibration, and joint position at the great toes, ankles, and knees, bilaterally providing categorical scores from 0 to 4 based on sensory levels.⁹ Symptoms (paresthesias, numbness, and neuropathic pain) were each rated on a similar 4-point scale. We defined *possible HSN* as decreased sensation of at least 1 modality in both lower extremities or a decrease or absence of ankle reflexes when compared with the patellar reflex and *probable*

HSN more stringently as decreased sensation of at least 1 modality in both lower extremities and a decrease or absence of ankle reflexes. Subjects meeting criteria for *HSN* who had symptoms were categorized as symptomatic *HSN*. Differences between subjects with and without *HSN* were assessed by Mann-Whitney test for 2 independent samples for continuous variables and by χ^2 test or Fisher exact test for dichotomous variables.

Most subjects had advanced HIV disease with a median (interquartile range) CD4 count of 132 (24–320) cells per deciliter, and 37% had a past AIDS-defining opportunistic illness, most frequently tuberculosis (19%). Thirty-seven subjects (37%) were ARV-naïve. Among those treated, 61 (97%) were on 3-drug combination potent ARV therapy with 94% on dNRTI-containing regimens. The ARV-experienced subgroup was slightly older (38 vs. 35 years, $P=0.04$), and the median body mass index was slightly higher than in the ARV-naïve subgroup (21 vs. 19.7, $P=0.04$). The ARV-experienced subgroup, on average, had a higher CD4 count (217 vs. 44, $P<0.001$), and among cases where data were available (22/63), 55% had undetectable plasma HIV RNA levels.

Symptoms possibly suggestive of neuropathy were noted in 13 (35%) of 37 ARV-naïve subjects and in 22 (35%) of 63 ARV-experienced subjects. Interestingly, neuropathic pain was a symptom found only in ARV-experienced subjects (7/63 ARV-experienced patients compared with 0/37 ARV-naïve patients). Six (16%) of 37 ARV-naïve subjects and 10 (16%) of 63 ARV-experienced subjects had 1 or more bilateral signs suggestive of neuropathy. Possible neuropathy criteria were met in 12 (32%) of 37 ARV-naïve patients and in 16 (25%) of 63 ARV-experienced subjects for an overall rate of 28%. Only 10 subjects (10%) met the stringent study-defined criteria for probable *HSN* (Table 1). All were symptomatic. The rate of probable *HSN* did not differ between the ARV-naïve (4/37 subjects, 10.6%) and ARV-experienced (6/63 subjects, 9.5%) subgroups. No differences in sex, age, or body mass index were noted between subjects with or without *HSN* in either the ARV-naïve or ARV-experienced subgroups. A lower CD4 lymphocyte count was associated with higher risk of *HSN* in the cohort as a whole and specifically in the ARV-experienced subgroup with a similar trend in the ARV-naïve subgroup. A trend toward lower HIV viral load as a risk factor for *HSN* was observed in the ARV-experienced cohort. We identified no difference in dNRTI exposure between those with and without *HSN* ($P=0.34$); although 94% were on dNRTI-based treatment.

In other reports, rates of *HSN* have varied widely, likely due to multiple factors including differences in *HSN* definitional criteria, variations in HIV stage, possible differences in host and viral clade parameters, and variation in rates, types, and duration of ARV treatments. Our protocol employed a strict definition determined by neurological evaluations conducted by neurologists and identifies an overall 10% frequency that does not differ by ARV status. The subjects were all Thai and were most likely infected with recombinant circulating form (CRF) 01_AE, the predominant HIV subtype found in Bangkok.¹⁰ The study is limited by the lack of statistical power due to its small sample size and by the incomplete immunovirologic information. However, it is interesting to note a lack of difference in probable *HSN* rates by ARV status. This finding is unexpected considering the high frequency of dNRTI use (94%), a factor expected to increase rates of antiretroviral toxic neuropathy. Although many studies have reported high rates of *HSN* up to 55% with dNRTI, other studies have reported a lower prevalence.^{4,11–13} Therefore, it is tempting to hypothesize that in our cohort, the tendency of dNRTI to induce neuropathy may have been outweighed by the favorable effects of immunologic benefit with potent ARV therapy, particularly because our cohort had severe immunosuppression. A careful prospective evaluation of *HSN* before and after use of both dideoxynucleoside-containing and nondideoxynucleoside-containing ARV regimens may be warranted.

In terms of immunovirologic parameters, a trend for low CD4 count in association with HSN was found in the cohort as a whole and specifically among ARV-experienced subjects. This finding is similar to that reported in the HIV Outpatient Study and suggests that immunologic parameters continue to be important as a risk factor for HSN after use of potent ARV medications.¹⁴ The association of low HIV RNA levels with HSN in the ARV-experienced cohort may reflect better HIV medication adherence and increase exposure to the dideoxynucleoside medications; however, it is also notable that virological data were very limited.

In summary, this study found an overall frequency of probable HSN at 10% and that of possible HSN at 28% among HIV-infected subjects attending an outpatient ID clinic in Bangkok, Thailand. Rates of HSN were comparable between ARV-naïve and ARV-experienced subjects, despite the heavy use of dideoxynucleoside-containing medications in ARV-experienced subjects. Low CD4 count was a risk factor for HSN in general and specifically in ARV-experienced subjects. Further studies are warranted to prospectively evaluate the changes in rates of HSN after highly active antiretroviral therapy initiation with both dideoxynucleoside-containing and nondideoxynucleoside-containing regimens.

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TABLE 1

Demographic and HIV-Related Information Comparing Subjects With and Without Probable HSN for the Entire Cohort and Separately Among ARV-Naive and ARV-Experienced Subgroups

	Entire Cohort (n = 100)				ARV-Naive (n = 37)				ARV-Experienced (n = 63)			
	No HSN (n = 90)	HSN (n = 10)	P		No HSN (n = 33)	HSN (n = 4)	P		No HSN (n = 57)	HSN (n = 6)	P	
Demographics												
Sex (male %)	44	60	0.27		36	75	0.28		49	50	1.00	
Age (yrs) median (IQR)	37 (30-44)	35 (32-47)	0.87		34 (27-41)	36 (29-46)	0.75		38 (32-45)	34 (32-47)	0.73	
Body mass index (kg/m ²) median (IQR)	20.6 (19.0-22.5)	20.8 (18.7-22.6)	0.98		19.4 (17.5-21.5)	20.3 (19.8-22.5)	0.36		21.0 (19.6-22.6)	21.4 (16.9-22.7)	0.72	
HIV variables												
Current CD4 count (within 3 mos, if available) median (IQR)	155 (44-324) (n = 75)	28 (8-203) (n = 10)	0.01		54 (14-102) (n = 23)	10 (5-38) (n = 4)	0.08		222 (91-396) (n = 52)	71 (8.3-184) (n = 6)	0.05	
Log HIV RNA (within 3 mos, if available) median (IQR)	4.78 (1.70-5.70) (n = 31)	1.7 (1.7-5.3) (n = 6)	0.12		5.6 (5.1-5.8) (n = 13)	5.4 (4.0-6.6) (n = 2)	0.80		2.1 (1.70-4.9) (n = 18)	1.7 (1.7-1.7) (n = 4)	0.06	
% with history of AIDS-defining illness	36	50	0.29		33	50	0.60		37	50	0.67	

IQR, interquartile range.