

ABSTRACT

Background: Peripheral neuropathy (PN) is the most frequent neurological complication in HIV infection. Symptoms including pain, numbness, and "pins and needles" sensation, affect quality of life, often require analgesic therapy and may influence the choice of antiretroviral (ARV) drugs. No FDA-approved therapy exists. While pre-HAART risk factors for PN included high HIV-1 RNA, low CD4, and neurotoxic ARV (d-drug) use, risk factors in the HAART era are not well delineated. Objectives of this study include estimating the prevalence of neuropathic signs and symptoms with ARV initiation in ARV-naïve patients and investigating prognostic factors in the HAART era.

Methods: Participants from the ACTG A5001 cohort that initiated HAART in randomized trials for ARV-naïve patients were annually administered a brief PN screen by trained site personnel, evaluating symptoms and signs of PN between January 2000 and June 2007. HIV-1 RNA, CD4, d-drug and PI use were concurrently collected longitudinally. PN was defined as at least mild loss of vibration sensation in both great toes bilaterally or absent or hypoactive ankle reflexes bilaterally relative to knees. Symptomatic PN (SPN) was defined as PN plus bilateral symptoms. Multivariate logistic generalized estimating equation regression models were used to estimate associations with PN and SPN while controlling for potential confounders.

Results: 2135 ARV-naïve participants (81% male, 44% white, 32% black, median age=39, median log HIV-1 RNA at HAART initiation=9) were analyzed. d-drug use peaked at week 144 (25%) dropping to 10.9% at week 384. The increasing prevalences of PN and SPN after HAART initiation are summarized below:

PREVALENCES OF PN AND SPN AFTER HAART INITIATION						
Week after HAART Initiation	When CD4>350			When HIV-1 RNA<400		
	N	PN(%)	SPN(%)	N	PN(%)	SPN(%)
48	768	25.7	8.2	1253	29.5	10.1
96	1042	29.9	7.9	1389	32.1	8.7
192	889	33.1	8.8	1053	33.5	9.6
288	494	37.9	11.7	556	41.5	14.0
384	287	41.5	13.6	331	44.4	14.2

Notable factors associated with PN included: year since HAART-initiation (p<0.01, OR=1.09 for each additional year, 95% CI=1.06, 1.12)), age (p<0.01, OR=1.89 for a 10 year increase, 95% CI=1.72, 2.06)), and d-drug use (p<0.01, OR=1.51, (1.30, 1.75)).

Conclusions: The prevalence of PN and SPN increases with time after ARV initiation in ARV-naïve patients despite increased virologic control and immune function, and the decline of d-drug use. Age and d-drug use are notable risk factors for PN and SPN.

BACKGROUND

Sensory neuropathies (SNs) are the most frequent neurological disorder associated with HIV infection and its treatment with ARVs.

There are two major types of HIV-associated peripheral SN, distal sensory polyneuropathy (DSP) and ARV toxic neuropathy (ATN) which affect approximately 30%-67% of patients with advanced HIV disease. DSP is the most common SN in HIV infection. ATN is the most common toxicity of ARV therapy in Sub-Saharan Africa.

The most common symptom of HIV-SN is pain. Other symptoms include numbness, paresthesia, or burning sensation. Common signs include reduced or absent ankle reflexes with intact patellar reflexes, reduced or absent vibration sensation in the toes, and decreased pin and temperature sensation in a stocking/glove distribution.

No FDA approved therapies exist for HIV-associated SNs with treatment limited to symptomatic measures.

Higher plasma HIV-1 RNA levels and lower CD4+ cell counts before the initiation of ARV therapy appeared to increase the risk of DSP in the pre-HAART era. Prolonged exposure to HAART, protease inhibitor (PI) exposure, and lipid lowering drugs (statins and fibrates) have been suggested as risk factors for neuropathy in the HAART era.

METHODS

Participants were selected from the AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT A5001) trial, a meta-study comprised of participants prospectively enrolled into randomized clinical trials. Study participants include those that have agreed to be followed long-term for the purpose of evaluating clinical, virologic, immunologic, and neurologic outcomes associated with treatment of HIV with potent ARVs. All available data for ARV-naïve participants for which neuropathy-related data had been collected were included.

Neuropathy Data

The Brief Peripheral Neuropathy Screen (BPNS) is administered in A5001 every 48 weeks by trained site personnel (not neurologists). The BPNS assesses signs (vibration sensation and ankle reflexes) and symptoms (pain, "pins and needles", and numbness). The performance characteristics of the BPNS have been studied (Simpson 2006, Ellis 2005). PN was defined as at least mild loss of vibration sensation in both great toes bilaterally or absent or hypoactive ankle reflexes bilaterally relative to knees. Symptomatic PN (SPN) was defined as PN plus bilateral symptoms. Painful PN (PPN) was defined as PN plus pain symptoms. Use of d-drug or PIs was defined as at least 4 weeks of use within the last 6 months of evaluation.

Objectives

To describe the prevalence and incidence of neuropathy in ARV-naïve patients after initiation of combination ARV therapy.
 To identify prognostic factors associated with PN in ARV-naïve patients after initiation of combination ARV therapy

Statistical Methods

Graphical methods are utilized to display the prevalence of PN, neuropathic signs and symptoms, and ARV use over time as well as to summarize odds ratios and associated confidence intervals for risk factors for PN and SPN. Logistic generalized estimating equation (GEE) regression models are used to estimate the association (odds ratios and associated confidence intervals) between potential risk factors (e.g., d-drug use, PI use, demographic variables, HIV-1 RNA, CD4, CD4 nadir, time since initiation of combination ARVs, etc.) and PN.

RESULTS

Demographics and Baseline Characteristics

2135 ARV-naïve participants (81% male, 44% white, 32% black, median age=39 years, median log HIV-1 RNA =4.9 and median CD4 count = 206 at HAART initiation) were analyzed.

BASELINE LOG10 (HIV-1 RNA) VIRAL LOAD

	Total
N	2,135
# missing	0
Log10 (RNA VL), (cp/ml)	
Mean	4.95
Standard deviation	0.76
Min, Max	1.96, 7.11
Median	4.90
Q1, Q3	4.46, 5.51

BASELINE CD4 COUNT

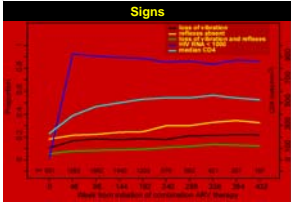
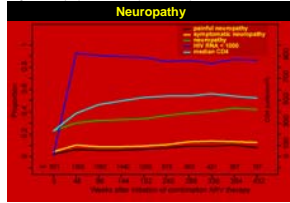
	Total
N	2,133
# missing	2
Mean	235.8
Standard deviation	199.3
Min, Max	0, 1,513
Median	206
Q1, Q3	60, 350

DEMOGRAPHICS

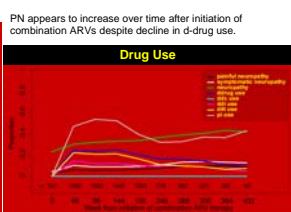
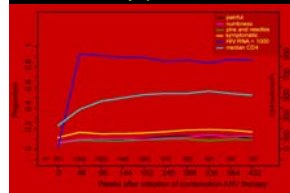
	Total (N=2135)	
	Median	39
	10-19	6 (0%)
	20-29	263 (12%)
	30-39	864 (40%)
	40-49	696 (33%)
	50-59	238 (11%)
	Over 60	68 (3%)
Gender	Male	1736 (81%)
	Female	399 (19%)
Race/Ethnicity	White	949 (44%)
	Black	693 (32%)
	Other	493 (23%)
IV drug history	No	1929 (90%)
	Yes	206 (10%)
HCV seropositivity	positive ever	208 (10%)
	Negative	1764 (83%)
	Not available	163 (8%)

Prevalence

Signs and symptoms of PN persist despite viral control and improved immune function with initiation of combination ARVs.



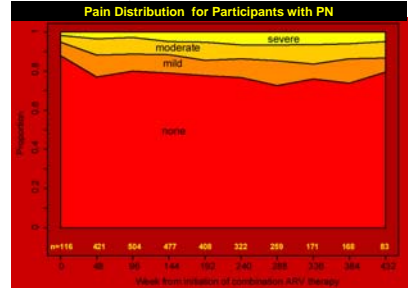
Symptoms



RESULTS CONTINUED

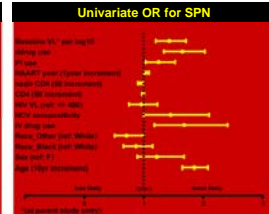
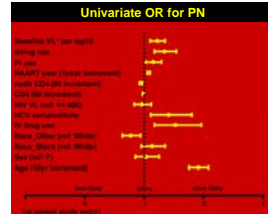
Pain Levels

Most PN occurs without pain.



Risk Factors

Increased age, d-drug use, and higher baseline HIV-1 RNA are univariately associated with increased risk of PN and SPN.



PREVALENCE						
		When CD4 > 350			When VL <= 400	
ALLRT week	N	Neuropathy % (95% CI)	Symptomatic Neuropathy % (95% CI)	N	Neuropathy % (95% CI)	Symptomatic Neuropathy % (95% CI)
0	139	26.6 (19.5, 34.8)	2.9 (0.8, 7.2)	0	---	---
48	768	25.7 (22.6, 28.9)	8.2 (6.4, 10.4)	1253	29.5 (27.0, 32.1)	10.1 (8.5, 11.9)
96	1042	29.9 (27.2, 32.8)	7.9 (6.3, 9.7)	1389	32.1 (29.7, 34.6)	8.7 (7.3, 10.3)
144	1004	30.2 (27.4, 33.1)	7.8 (6.2, 9.6)	1256	32.9 (30.3, 35.6)	8.8 (7.3, 10.5)
192	889	33.1 (30.0, 36.3)	8.8 (7.0, 10.8)	1053	33.5 (30.7, 36.5)	9.6 (7.9, 11.5)
240	673	35.1 (31.5, 38.8)	9.8 (7.7, 12.3)	731	37.3 (33.8, 41.0)	10.9 (8.8, 13.4)
288	494	37.9 (33.6, 42.3)	11.7 (9.0, 14.9)	556	41.5 (37.4, 45.8)	14.0 (11.2, 17.2)
336	304	38.2 (32.7, 43.9)	12.5 (9.0, 16.8)	347	40.6 (35.4, 46.0)	13.5 (10.1, 17.6)
384	287	41.5 (35.7, 47.4)	13.6 (9.8, 18.1)	331	44.4 (39.0, 49.9)	14.2 (10.6, 18.4)
432	135	37.8 (29.6, 46.5)	11.1 (6.4, 17.7)	169	40.8 (33.3, 48.6)	12.4 (7.9, 18.4)

ACKNOWLEDGEMENTS

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Multivariate modeling suggests notable factors associated with PN include age (OR=1.89, 95% CI=(1.72, 2.06)), d-drug use (OR=1.51, 95% CI=(1.30, 1.75)), and log10 baseline HIV-1 RNA (OR=1.13, 95% CI=(1.02, 1.26)). The multivariate model also included race, CD4 count, PI use, and years since HAART initiation.

Multivariate modeling suggests notable factors associated with SPN include age (OR=1.89, 95% CI=(1.67, 2.13)), d-drug use (OR=1.84, 95% CI=(1.49, 2.28)), and log10 baseline HIV-1 RNA (OR=1.35, 95% CI=(1.13, 1.62)). The multivariate model also included gender.

CONCLUSIONS

Neuropathic signs persist despite improved immunologic function and viral control associated with combination ARVs.

Signs frequently occur without pain.

Age, d-drug use, PI use, year since initiation of anti-HIV therapy, IV drug use, HCV seropositivity, and baseline HIV-1 RNA are associated with PN and SPN.

Limitations of this study include its observational nature with the potential for informative drop-out/in, self-selection issues in ARV use (e.g., d-drug use), and that the observed association may not be causal.