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SHORT COMMUNICATION

HIV peripheral neuropathy progression: protection with glucose-lowering drugs?

Scott R. Evans · Anthony J. Lee · Ronald J. Ellis · Huichao Chen · Kunling Wu · Ronald J. Bosch · David B. Clifford

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Abstract The purpose of this study is to evaluate risk factors for progression from asymptomatic peripheral neuropathy (APN) to symptomatic peripheral neuropathy (SPN). Antiretroviral therapy (ART)-naïve patients initiating combination ART were followed longitudinally and screened for signs/symptoms of PN. Having APN was associated with higher odds of future SPN (odds ratio (OR)=1.58, 95 % confidence interval (CI)=(1.08, 2.29), p=0.027). Neurotoxic ART use was associated with increased odds of progression to SPN (OR=2.16, 95 % CI=(1.21, 3.85), p=0.009) while use of glucose-lowering drugs (non-insulin) was protective (OR=0.12, 95 % CI=(0.02, 0.83), p=0.031). Use of glucose-lowering drugs (non-insulin) may prevent progression from APN to SPN.

Keywords Peripheral neuropathy · Symptomatic peripheral neuropathy · Risk factors · HIV · Glucose-lowering drugs

S. R. Evans
Center for Biostatistics in AIDS Research, Department of Biostatistics, FXB-513 Harvard School of Public Health,
651 Huntington Avenue,
Boston, MA 02115, USA

A. J. Lee (✉)
Center for Biostatistics in AIDS Research, Department of Biostatistics, FXB-543 Harvard School of Public Health,
651 Huntington Avenue,
Boston, MA 02115, USA
e-mail: evans@sdac.harvard.edu

R. J. Ellis
Department of Neurosciences,
University of California at San Diego,
San Diego, CA, USA

H. Chen · K. Wu · R. J. Bosch
Center for Biostatistics in AIDS Research, Department of Biostatistics, Harvard School of Public Health,
651 Huntington Avenue,
Boston, MA 02115, USA

D. B. Clifford
Department of Neurology, Washington University,
Saint Louis, MO, USA

Introduction

Although combination antiretroviral therapy (cART) has resulted in declines in the incidence of CNS disease in HIV, sensory neuropathies (SNs) are still prevalent and one of the most frequent neurological disorder associated with HIV infection and its treatment with antiretroviral therapy (ART) (Evans et al. 2011; McArthur et al. 2005; Ellis et al. 2009).

There are two major types of HIV-associated distal sensory peripheral neuropathies: primary HIV-associated distal sensory polyneuropathy (HIV-DSP) and ART toxic neuropathy (ATN) together affect approximately 30–67 % of patients with advanced HIV disease (Wulff et al. 2000; Cornblath and McArthur 1988). HIV-DSP is the most common SN in HIV infection with a reported 1-year incidence in an advanced patient cohort selected for neurologic disease risk of 36 % in the pre-cART era as compared to 21 % in the cART era (Schifitto et al. 2005). ATN is associated with neurotoxic ART (nART), e.g., dideoxynucleoside analogues and shares most clinical features of HIV-DSP except that neuropathy develops while taking the nART. ATN is the most common toxicity of ART therapy in sub-Saharan Africa (Wulff et al. 2000; Cornblath and McArthur 1988; Forna et al. 2006; Kim et al. 2006; Simpson et al. 2006a).

The signs/symptoms of HIV-DSP and ATN resemble common distal sensory neuropathies encountered in clinical practice including diabetic and alcohol-associated

neuropathy. Symptoms include numbness, paresthesia, burning sensation, and stabbing pain especially in the feet. Common signs include reduced or absent ankle reflexes relative to 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 with limited efficacy.

Risk factors for peripheral neuropathy (PN) and symptomatic peripheral neuropathy (SPN) in the cART era have been evaluated previously (Evans et al. 2011). In this study, we evaluated potential risk factors for progression from asymptomatic peripheral neuropathy (APN) to SPN using data from ART-naïve patients who had recently initiated cART in six randomized AIDS Clinical Trials Group (ACTG) trials.

Methods

Participants were selected from the ACTG Longitudinal Linked Randomized Trials (ALLRT), a meta-study of participants prospectively enrolled into randomized clinical trials of cART (at least three ARTs) regimens (Smurzynski et al. 2008). Study participants include those that agreed to be followed long-term for the purpose of evaluating clinical, virologic, immunologic, and neurologic outcomes associated with treatment of HIV with cART. All patient time-points for which a neurological evaluation was performed were included in analyses. Demographics and ART use were also collected. Study participants had different follow-up and timing (relative to initiation of cART) for their first neurologic evaluations, and the median time from ART initiation to first evaluation was 48 weeks. Participants from six randomized trials (ACTG trials 347 (Eron et al. 2000), 384 (Robbins et al. 2003), 388 (Fischl et al. 2003), A5014 (Landay et al. 2003), A5095 (Gulick et al. 2004), and A5142 (Riddler et al. 2008)) were analyzed.

Peripheral neuropathy data

The Brief Peripheral Neuropathy Screen (BPNS) was administered in ALLRT every 48 weeks by trained non-neurologist site personnel. The BPNS assesses signs (vibration sensation at the feet and ankle reflexes) and symptoms (pain, "pins and needles" sensation, and numbness). The performance characteristics of the BPNS have been reported (Simpson et al. 2006b; Ellis et al. 2005).

PN was defined as at least mild loss of vibration sensation in both great toes or absent or hypoactive ankle reflexes bilaterally relative to knees. SPN was defined as APN plus any bilateral symptoms. APN was defined as PN without bilateral symptoms. Use of nART or PIs was defined as at least 4 weeks of use within 6 months prior to the evaluation.

Objectives

Objectives of this study include:

1. To estimate the association between APN with future SPN
2. To estimate the association between potential risk factors with progression from APN to SPN
3. To estimate the association between potential risk factors with progression from no PN to APN and SPN

Statistical methods

Multivariable logistic regression models (logistic generalized estimating equation (GEE) with AR1 working covariance matrix) were used to estimate the association (i.e., odds ratios and associated confidence intervals) between potential risk factors for progression from APN to SPN. Multivariable models included all of the risk factors described below since there was interest in estimating the association between each of these variables with progression from APN to SPN. Model fit was assessed using methods described in Evans et al. (Evans and Li 2005). A forest plot summarizes these odds ratio estimates and associated confidence intervals.

Reported model results are from "full" models including all covariates, and thus odds ratio estimates are adjusted for other variables. Variables included in the models were demographics, HIV disease characteristics, ART use at the time of the evaluation, concomitant therapy use, and other patient characteristics.

Demographic variables included: age at the time of evaluation (scaled such that odds ratios are interpreted for a 10-year increment), race (white (reference), black, Hispanic, other), sex (reference = male), and height at cART initiation (scaled such that odds ratios are interpreted for a 5-cm increment). HIV disease characteristics variables included: $\log_{10}$ (HIV-1 RNA) at cART initiation, CD4 at cART initiation: (categories: ≤200, 201–350, 351–500, ≥501 (reference)), HIV-1 RNA at the time of evaluation (categories: ≤400 (reference), >400), CD4 at the time of evaluation: (categories: ≤200, 201-350, 351-500, ≥501 (reference)), and years since cART initiation. ART use at the time of the evaluation variables included: nART use (i.e., use of d4T, ddI, or ddC) and PI use. Concomitant therapy use variables included: the use of a statin drug within the previous 21 days of the evaluation, the use of a non-statin lipid-lowering drug within the previous 21 days of the evaluation, the use of insulin within the previous 21 days of the evaluation, and the use of a glucose-lowering drug (non-insulin) within the previous 21 days of the evaluation. Other patient characteristics included: reported history of diabetes, HCV seropositivity, and history of intravenous drug use.

Table 1 Demographics and baseline characteristics

Characteristic		Model 1 (N=1,592)[a]	Model 2 (N=374)[b]	Models 3 and 4 (N=1,218)[c]
Age at first neurologic assessment	10–19	8 (1 %)	1 (0 %)	7 (1 %)
	20–29	267 (17 %)	42 (11 %)	225 (18 %)
	30–39	670 (42 %)	114 (30 %)	556 (46 %)
	40–49	475 (30 %)	144 (39 %)	331 (27 %)
	50–59	139 (9 %)	52 (14 %)	87 (7 %)
	Over 60	33 (2 %)	21 (6 %)	12 (1 %)
Sex	Male	1,280 (80 %)	298 (80 %)	982 (81 %)
	Female	312 (20 %)	76 (20 %)	236 (19 %)
Race	Other	37 (2 %)	80 (21 %)	293 (24 %)
	Hispanic	336 (21 %)	N/A	N/A
	Black	502 (32 %)	135 (36 %)	367 (30 %)
	White	717 (45 %)	159 (43 %)	558 (46 %)
IV Drug history	No	1,466 (92 %)	332 (89 %)	1,134 (93 %)
	Yes	126 (8 %)	42 (11 %)	84 (7 %)
HCV seropositivity	Positive ever	161 (10 %)	50 (13 %)	111 (9 %)
	Negative	1,431 (90 %)	324 (87 %)	1,107 (91 %)
Pre-ART CD4 (cells/μL)	Number	1,592	374	1,218
	Mean (s.d.)	239 (196)	214 (192)	247 (197)
	Median	213	166	224
	Q1, Q3	68, 351	50, 324	76, 362
Pre-ART log10 (HIV RNA), (cp/mL)	Number	1,592	374	1,218
	Mean (s.d.)	4.92 (0.75)	5.00 (0.73)	4.90 (0.76)
	Median	4.87	4.91	4.85
	Q1, Q3	4.44, 5.46	4.48, 5.58	4.43, 5.43

s.d. standard deviation

[a] Model 1 = APN risk factor for future SPN

[b] Model 2 = Risk factors for SPN from APN

[c] Models 3 and 4 = Risk factors for APN and SPN from no PN

Results

Association between APN and progression to future SPN (model 1)

To estimate the association between APN and future SPN, we restricted analyses to only those participants without SPN at their first neurologic visit while on cART. One thousand five hundred ninety-two ART-naïve participants (80 % male, 45 % white, 32 % black, 42 % were 30–39 years of age, median $\log_{10}$ HIV-1 RNA=4.9 cp/mL, and median CD4 count=213 cell/mm^3 at cART initiation) were analyzed (Model 1, Table 1). Data from 5,178 participant visits were included. The average duration of follow-up was 255 weeks (s.d. = 103; median (min, max) visits per patient was 3 (1, 8)), and there were 282 (5.5 %) patient time-points for which SPN was observed. Logistic GEE models were used to estimate the association between the APN status at the first visit with future SPN status. Having APN (vs. not having APN) was associated with higher odds of future SPN (odds ratio (OR)=1.58, 95 % confidence interval (CI)=(1.08, 2.29), p=0.027). Other variables associated with higher odds of future SPN included age (OR=1.43 per 10-year increment, 95 % CI=(1.20, 1.71), p< 0.001), current nART use (OR=1.96, 95 % CI=(1.41, 2.73), p <0.001), and years since cART initiation (OR=1.13 per 1 year, 95 % CI=(1.05, 1.20), p=0.001). For 374 participants with APN at their first visit, 11 (2.9 %), 50 (13.4 %), and 313 (83.7 %) displayed SPN at all, some, or no follow-up visits, respectively. These participants had 1,282 follow-up time-points, of which 105 (8.2 %) displayed SPN and 1,177 (91.8 %) displayed no SPN. For the 1,218 patients without APN at their first visit, 13 (1.1 %), 99 (8.1 %), and 1,106 (90.8 %) patients displayed SPN at all, some, or no follow-up visits, respectively. These participants had 3,896 time-points of which 177 (4.5 %) displayed SPN and 3,719 (95.5 %) displayed no SPN.

Associations with progression from APN to SPN (model 2)

To evaluate risk factors for progression from APN to SPN, we restricted analyses to those participants with APN at their first neurologic visit while on cART. We then used data from subsequent visits to evaluate associations with SPN. Three hundred seventy-four 374 ART-naïve participants (80 % male, 43 % white, 36 % black, 39 % were 40–49 years of age, and 30 % were 30–39 years of age, median $\log_{10}$ HIV-1 RNA=5.00 cp/mL, and median CD4 count=166 cell/mm^3 at cART initiation) were analyzed (Model 2, Table 1). For 374 patients analyzed, median (min, max) visits per patient was 3 (1, 8).

In a multivariable model (Fig. 1), nART use was associated with increased odds of progression from APN to SPN (OR=2.16, 95 % CI=(1.21, 3.85), p=0.009) while use of a glucose-lowering drug (non-insulin) was protective (OR=0.12, 95 % CI=(0.02, 0.83), p=0.031). Of 28 time-points with patients on a glucose-lowering drug, only one instance of SPN (3.6 %) was observed while of 1,254 time-points with patients not on a glucose-lowering drug, 104 instances of SPN (8.3 %) were observed. There were 21 diabetic patients (reported history of diabetes) with 63 patient visits. Out of 21 diabetic patients, eight (38.1 %) and 13 (61.9 %) patients were on non-insulin glucose-lowering agents at all and some follow-up visits, respectively, while four (19.1 %) and 17 (81.0 %) patients were on insulin glucose-lowering agents at all and some follow-up visits, respectively. Out of 23 time-points for diabetic patients on non-insulin glucose-lowering drugs, only one case of SPN (4.6 %) was observed while out of 11 time-points for diabetic patients on insulin glucose-lowering drugs, one case of SPN (9.1 %) was also observed. Out of 40 time-points for diabetic patients not on non-insulin glucose-lowering drugs, nine cases of SPN (22.5 %) were observed while out of 52 time-points for diabetic patients not on insulin glucose-lowering drugs, nine cases of SPN (17.3 %) were also observed. Although a history of diabetes did not reach statistical significance as a risk for progression, the data are consistent with a history of diabetes having a large magnitude of association with progression (OR=4.16, 95 % CI=(0.97, 17.96), p=0.056) (Fig. 1).

Associations with progression from no PN to APN and SPN (models 3 and 4)

To evaluate risk factors for progression from no PN to APN as well as no PN to SPN, we restricted analyses to those participants with no PN at their first neurologic visit while on cART. We then used data from subsequent visits to

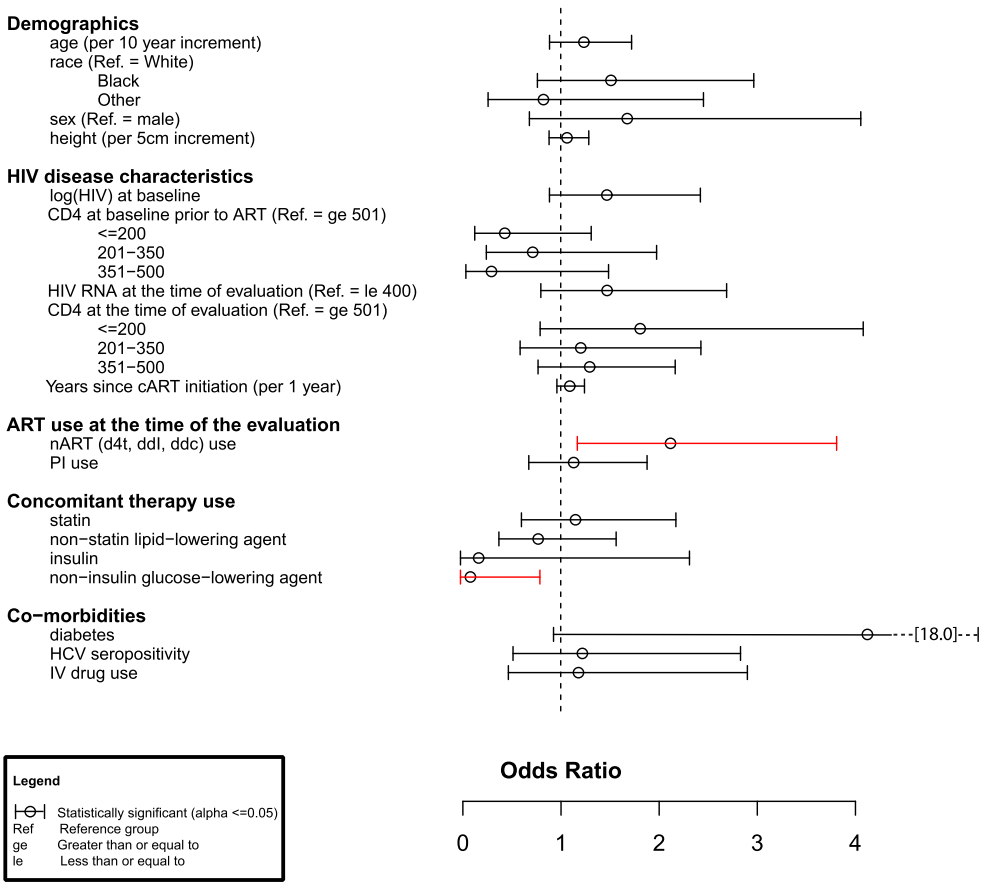

Fig. 1 Odds ratio estimates (95% CI) for predictors of future SPN from APN

evaluate associations with APN and SPN. One thousand two hundred eighteen ART-naïve participants (81 % male, 46 % white, 30 % black, 46 % were 30–39 years of age, and 27 % were 40–49 years of age, median $\log_{10}$ HIV-1 RNA=4.85 cp/mL, and median CD4 count=224 cell/mm^3 at cART initiation) were analyzed (Models 3 and 4, Table 1). The following variables were associated with increased odds of progression from no PN to APN: age (OR=1.46 per 10-year increment, 95 % CI=(1.29, 1.66), $p<0.001$), current nART use (OR=1.45, 95 % CI=(1.16, 1.81), $p=0.002$), height (OR=1.12, 95 % CI=(1.04, 1.21), $p=0.005$), and years since cART initiation (OR=1.09 per 1 year, 95 % CI=(1.04, 1.14), $p<0.001$). The following variables were associated with increased odds of progression from no PN to SPN: age (OR=1.69 per 10-year increment, 95 % CI=(1.36, 2.10), $p<0.001$), current nART use (OR=1.91, 95 % CI=(1.26, 2.90), $p=0.006$), and years since cART initiation (OR=1.11 per 1 year, 95 % CI=(1.02, 1.20), $p=0.020$).

Discussion

Peripheral neuropathy in HIV patients persists despite improved immunologic function and virologic control associated with cART and decreased nART use (Evans et al. 2011). Symptomatic neuropathy disturbs quality of life. However, a mild decrease in peripheral conduction efficiency reflected by decreased vibration sensation in the toes, or reduced ankle reflexes, may have minimal functional consequences. However, if asymptomatic neuropathy predicts evolution to clinically important symptomatic sensory neuropathy, then protective or regenerative strategies will be important. These considerations are of considerable importance given the large pool of HIV patients with asymptomatic neuropathy. Our findings indeed indicate that the likelihood of developing symptomatic sensory neuropathy is increased in those with asymptomatic dysfunction. Neurotoxic drugs are particularly hazardous in those with these underlying findings, suggesting that prior to prescribing such drugs, a neurological exam is warranted.

A surprising finding is that non-insulin diabetic therapy appears to reduce the odds of converting to symptomatic sensory neuropathy. One might have predicted the opposite finding, since diabetes is often the strongest risk for developing neuropathy (Evans et al. 2011), yet a therapy that would be used only in a diabetic population is associated with decreased risk. Mechanisms for this are speculative beyond better glucose control, but might include prevention of oxidative stress neuronal injury that may drive neuropathy as well as other neurodegenerative conditions (El-Mir et al. 2008). The potential that treatment of diabetes is particularly important in the setting of HIV is suggested by our results. A very strong trend towards developing symptomatic neuropathy is seen in diabetic patients, whereas treatment with non-insulin glucose-lowering agents is protective, and if anything there is a trend to protection in those treated with insulin. The findings suggest that there might even be neuroprotective properties to oral hypoglycemic, since it is unlikely that glucose control in this population would have exceeded that of non-diabetic patients. If tolerable low doses of hypoglycemic mimicked this apparent neuroprotection, it could be a finding of considerable importance.

Limitations of this study include its observational nature with the potential for informative dropout/in, self-selection issues in ART and concomitant medication use, the observed association may not be causal, and a limited number of observations in diabetics on non-insulin hypoglycemic drugs. Estimated association with variables subject to self-selection should be interpreted with caution. Non-significant p values should not be interpreted as "no association." Instead the confidence intervals should be used to "rule out" associations with reasonable confidence. Some effect estimates, although not significant, cannot rule out potentially large associations.

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