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## Patterns of peripheral neuropathy in ART-naïve patients initiating modern ART regimen

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### Abstract

**Objectives**—To evaluate associations of pre-ART CD4 with peripheral neuropathy (PN) and estimate the prevalence of PN in HIV positive patients starting modern combination antiretroviral therapy (cART) regimens.

**Methods**—ART-naïve subjects initiating cART were followed longitudinally and screened for signs/symptoms of PN.

**Results**—Lower pre-ART CD4 count was associated with post-ART PN. After 7 years (n=117), the prevalence (95% CI) of PN and SPN were 31% (23%, 40%) and 5% (2%, 11%) with pre-ART CD4 count > 250 copies/μL.

**Conclusion**—PN continues to be identified in HIV-infected individuals on modern cART by targeted assessment, but is generally without symptoms.

### Keywords

peripheral neuropathy; symptomatic peripheral neuropathy; risk factors; HIV; modern non-neurotoxic ART; higher pre-ART CD4 count

## INTRODUCTION

The advent of combination antiretroviral therapy (cART) has decreased the incidence of HIV-associated neurologic disorders, but distal sensory peripheral neuropathy (PN) remains problematic.<sup>1,2,3,4,5</sup> Two common etiologies of PN, ART-toxic neuropathy (ATN) and primary HIV-associated polyneuropathy (HIV-PN), together account for approximately 30–

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### Conflict of Interest

The authors declare that they have no conflict of interest.

67% of the advanced HIV infected population.<sup>6,7,8</sup> HIV-PN is the most common form of PN in HIV infected population with a reported 1-year incidence in an advanced patient cohort selected for neurologic disease risk of 36% and 21% in the pre-cART and cART eras, respectively.<sup>9</sup> In the early cART era, ATN contributed to the high prevalence of PN, primarily due to stavudine and to a lesser extent didanosine use.<sup>10,11</sup> However, with the infrequent use of these agents in the current era and the emphasis on early treatment of HIV prior to advanced immunodeficiency, the prevalence of PN has not been well-defined.

Clinical manifestations of HIV-PN and ATN are indistinguishable and resemble the signs and symptoms of neuropathies due to other etiologies such as diabetes and alcohol. 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. Common symptoms include numbness, paresthesias, a burning sensation, and stabbing pain, especially in the feet. Currently FDA-approved therapies do not exist for HIV-associated PN, and only treatments of modest efficacy are available to alleviate symptoms.<sup>12</sup>

Since stavudine and didanosine use were found to be a risk factors for PN, the examination of HIV-infected patients not exposed to these agents reflects the anticipated future prevalence of neuropathy.<sup>1,3</sup> In addition, pre-ART (nadir) CD4 count has been shown to be a strong predictor of PN.<sup>3</sup> As HIV-infected patients are initiated on ART at higher CD4 counts<sup>13,14</sup>, this trend may further reduce the incidence of PN.

In this study, we investigated the prevalence of PN and symptomatic PN (SPN) in ART-naïve HIV-positive subjects who had initiated non-neurotoxic cART (nART) in three randomized AIDS Clinical Trials Group (ACTG) trials.

## METHODS

Participants were selected from the ACTG Longitudinal Linked Randomized Trials (ALLRT), a prospective observational study of participants who continued follow-up after the completion of their randomized clinical trials of cART regimens within the ACTG.<sup>15</sup> Study participants had variable length of follow-up and variable timing (relative to start of new regimens) for their first neuropathy evaluations due to the time when they enrolled in ALLRT (while the study participants may have started in the ACTG parent study at week 0, the same participants may not have enrolled in ALLRT until later weeks).

Participants from three ACTG randomized trials were analyzed: A5095 (enrolled from 2001–2002)<sup>16</sup>, A5142 (enrolled 2003–2004)<sup>17</sup>, and A5202 (enrolled 2005–2007)<sup>18</sup>. The included participants were who had initial cART and first neurological evaluation without nART (stavudine or didanosine).

Initial cART for each of the cohort was as follows: A5095 (lamivudine(3TC) + zidovudine(ZDV)+efavirenz(EFV), abacavir(ABC)+3TC+ZDV, or ABC+3TC+ZDV +EFV), A5142 (3TC+tenofovir(TDF)+EFV, 3TC+TDF+lopinavir/ritonavir(LPV/r), 3TC +ZDV+EFV, 3TC+ZDV+LPV/r, or EFV+LPV/r), A5202 (ABC+3TC+EFV, ABC+3TC +atazanavir/ritonavir(ATV/r), emtricitibine(FTC)+TDF+EFV, or FTC+TDF+ATV/r).

## Neuropathy Data

The Brief Peripheral Neuropathy Screen (BPNS) was administered in ALLRT at entry, then at every 48 weeks afterwards by trained non-neurologist site personnel. The BPNS assessed 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 elsewhere.<sup>19,20</sup>

PN was defined as absent or hypoactive ankle reflexes or at least mild loss of vibration sensation in both of the great toe joints. SPN was defined as PN plus any bilateral symptoms. Painful neuropathy was defined as PN plus symptoms of pain in both of the feet or legs. Neuropathic outcomes included PN, SPN, painful neuropathy, loss of vibration, absent reflexes, loss of vibration and reflexes, symptom of pain, “pins and needles” sensation, and numbness.

## Objectives

The objectives of this study were:

1. To evaluate the association between pre-ART CD4 count and neuropathic outcomes.
2. To estimate the prevalence of PN and SPN in HIV-treatment naïve patients whose pre-ART CD4 count is greater than 250 cells/ $\mu$ L at initiation of non-neurotoxic cART.

## Statistical Methods

Descriptive statistics were used to summarize the study sample. Univariable and multivariable logistic models were used to evaluate the association [odds ratios (ORs) and associated confidence intervals (CIs)] between pre-ART CD4 and pre-ART (baseline) neuropathic outcomes in the entire study sample as well as in the subset of participants with a pre-ART CD4 > 250 cells/ $\mu$ L. Univariable and multivariable logistic regression models (logistic generalized estimating equation (GEE) with AR1 working covariance matrix) were used to estimate the association between pre-ART CD4 and post-ART (post-baseline) neuropathic outcomes. Prevalence with 95% CI of pre-ART neuropathic outcomes was plotted as a moving average function of pre-ART CD4. Longitudinal plots display the prevalence of PN and SPN over time since ART initiation.

Multivariable models were fit to obtain ORs adjusted for other variables. Variables included were demographics, HIV disease characteristics, protease inhibitor (PI) 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 ORs are interpreted for a 10 year increment), race [white (reference), black, Hispanic, other], sex (reference = male), and height at parent study entry (scaled such that odds ratios are interpreted for a 5 cm increment). HIV disease characteristics variables included:  $\log_{10}$ (HIV-1 RNA) at baseline (pre-ART), HIV-1 RNA at the time of evaluation [categories: <400 (reference), >400 copies/ml], and CD4 at the time of evaluation: [categories: <200, 201–350, 351–500,  $\geq$ 501 cells/ $\mu$ L(reference)]. Concomitant therapy variables included: the use a statin drug, a non-

statin lipid-lowering drug, insulin, and a non-insulin glucose-lowering drug, all within the previous 21 days of the evaluation. Other patient characteristics included: reported history of diabetes, HCV seropositivity and history of IV drug use.

## RESULTS

### Association between pre-ART CD4+ counts and pre-ART neuropathic outcomes

The evaluation of the associations between pre-ART CD4 and pre-ART neuropathic outcomes is based on data from 698 patients (86% male, 46% white, 30% black, 42% were 30–39 years of age, median pre-ART log<sub>10</sub> HIV-1 RNA = 4.70 copies/ml, and median pre-ART CD4 count = 238 cell/μL) (Table 1). In univariable logistic regression models, pre-ART CD4 was significantly associated with the following pre-ART neuropathic outcomes: SPN (OR=0.69 per 100 pre-ART CD4 increment, 95% CI=(0.52, 0.91), p=0.01) and numbness (OR=0.80; 95% CI=0.65, 0.98; p=0.03) (Table 2). In multivariable logistic regression models, these neuropathic outcomes were no longer significantly associated (p-values>0.05) with pre-ART CD4 (Table 2). \*(Of note: Table 2 summarizes the results for full-range of pre-ART CD4 counts but not for pre-ART CD4 > 250 copies/μL).

The study sample was then restricted to individuals with pre-ART CD4 > 250 copies/μL, and the evaluation of the associations between pre-ART CD4 and pre-ART neuropathic outcomes is based on data from 336 patients (87% male, 49% white, 24% black, 43% were 30–39 years of age, median pre-ART log<sub>10</sub> HIV-1 RNA = 4.53 cp/ml, and median pre-ART CD4 count = 368 cell/ mm<sup>3</sup> at cART initiation). In univariable logistic regression models, pre-ART CD4 was significantly associated with: pre-ART PN (OR=1.17 per 100 Pre-ART CD4 increment; 95% CI=1.01, 1.35; p=0.04); this was no longer significant in a multivariable model.

### Association between pre-ART CD4+ counts and post-ART neuropathic outcomes

The evaluation of the associations between pre-ART CD4 and post-ART neuropathic outcomes is based on data from 2,092 patients (82% male, 43% white, 33% black, 38% were 30–39 years of age, median pre-ART log<sub>10</sub> HIV-1 RNA =4.68 copies/ml, and median pre-ART CD4 count = 226 cell/ mm<sup>3</sup> at cART initiation), consisting of 7,487 patient-visits (Table 1). In univariable logistic regression models, pre-ART CD4 was significantly associated with the following post-ART neuropathic outcomes: PN (OR=0.93 per 100 pre-ART CD4 increment; 95% CI=0.89, 0.98, p=0.01), loss of vibration (OR=0.92; 95% CI=0.87, 0.97; p=0.003), absent reflexes (OR=0.94; 95% CI=0.88, 0.99; p=0.02), loss of vibration and reflexes (OR=0.89; 95% CI=0.82, 0.97; p=0.003), and numbness (OR=0.92; 95% CI=0.84, 0.99; p=0.03). In multivariable logistic GEE model, these neuropathic outcomes were no longer significantly associated (p-values > 0.05) with pre-ART CD4 (Table 2).

The study sample was then restricted to individuals with pre-ART CD4 > 250 cells/μL, and the evaluation of the associations between pre-ART CD4 and post-ART neuropathic outcomes and is based on data from 937 patients (83% male, 48% white, 27% black, 38% were 30–39 years of age, median pre-ART log<sub>10</sub> HIV-1 RNA =4.51 cp/ml, and median pre-

ART CD4 count = 349 cells/ $\mu$ L at cART initiation), consisting of 3,382 patient-visits. In univariable and multivariable logistic GEE models, post-ART neuropathic outcomes were not significantly associated ( $p$ -values  $> 0.05$ ) with pre-ART CD4.

### **Association between pre-ART CD4+ counts and post-ART neuropathy among virally suppressed subjects**

The following sub-analysis included the full range of pre-ART CD4 counts but only those subjects with HIV RNA VL  $\leq 50$  cp/ml at neuropathy assessments, and is based on data from 1,929 patients (82% male, 44% white, 31% black, 37% were 30–39 years of age, median pre-ART  $\log_{10}$  HIV-1 RNA = 4.68 copies/ml, and median pre-ART CD4 count = 229 cells/ $\mu$ L at cART initiation), consisting of 6,315 patient-visits (Table 1). In univariable logistic GEE models, pre-ART CD4 was significantly associated with the following post-ART neuropathic outcomes: PN (OR=0.94 per 100 pre-ART CD4 increment; 95% CI=0.88, 0.99;  $p=0.01$ ), loss of vibration (OR=0.91; 95% CI=0.85, 0.97;  $p=0.002$ ), absent reflexes (OR=0.94; 95% CI= 0.88, 1.00;  $p=0.04$ ), loss of vibration and reflexes (OR=0.86; 95% CI=0.79, 0.95;  $p<0.001$ ), and numbness (OR=0.91; 95% CI=0.83, 0.99;  $p=0.02$ ). In multivariable logistic GEE models, pre-ART CD4 was significantly associated with numbness (OR=0.90 per 100 pre-ART CD4 increment; 95% CI=0.81, 1.00;  $p=0.049$ ) (Table 2).

This study sample was then restricted to pre-ART CD4  $> 250$  copies/ $\mu$ L, and the evaluation of the associations between pre-ART CD4 and post-baseline neuropathic outcomes is based on appropriate data from 882 patients (83% male, 49% white, 26% black, 38% were 30–39 years of age, median pre-ART  $\log_{10}$  HIV-1 RNA = 4.51 cp/ml, and median pre-ART CD4 count = 347 cell/ $\text{mm}^3$  at cART initiation), consisting of 2,881 patient-visits. In univariable and multivariable logistic GEE models, pre-ART CD4 was not significantly associated with any of the post-ART neuropathic outcomes.

### **Prevalence of PN and SPN**

To estimate the prevalence of PN and SPN, we restricted the analysis to 996 participants whose pre-ART CD4 was greater than 250 cells/ $\mu$ L (84% male, 48% white, 27% black, 39% were 30–39 years of age, median pre-ART  $\log_{10}$  HIV-1 RNA = 4.52 copies/ml, and median pre-ART CD4 count = 350 cells/ $\mu$ L at cART initiation) (Table 1). Prior to the initiation of cART, the prevalence (95% CI) of PN and SPN were 19.6% (15.5%, 24.3%) and 2.4% (1.0%, 4.6%). While the prevalence of PN initially increased and then remained stable to about 30%, SPN was rarely encountered in this population (Figure 1A). When the study sample was restricted to subjects with week 0 (pre-ART) neuropathy evaluations, the prevalence of PN and SPN remained similar to the non-restricted study sample (Figure 1B). Among those with concurrent PN, the prevalence of SPN (95% CI) at cART initiation and after 432 weeks of follow-up after cART initiation were 12.1% (5.4%, 22.5%) and 20.0% (5.7%, 43.7%) respectively.

Plots of the prevalence of neuropathic variables as a function of pre-ART CD4 show a decrease in the prevalence of PN with an increase of CD4 count in the regions of 0 to 250 CD4 count (Figures 2–4).

## DISCUSSION

Signs of peripheral nerve injury persist in HIV-infected patients despite improved immunologic function and virologic control associated with earlier cART initiation and decreased nART use.<sup>3</sup> However, recent studies evaluating interventions for painful peripheral neuropathy suffered from slow enrollment, and clinicians anecdotally note decreasing complaints of neuropathy in their HIV clinics. The data in this study suggest that despite the presence of signs associated with peripheral nerve dysfunction, symptomatic PN is uncommon and does not increase over a period of as long as eight years after cART initiation in the absence of neurotoxic cART.

Our large database of HIV-infected participants, who were evaluated regularly during and after their participation in randomized treatment initiation studies in the ACTG, is a valuable means of describing peripheral nerve involvement in HIV-infected populations in the current treatment era. Peripheral nerves are delicate and easily injured cells that may be damaged by inflammatory responses during chronic infection including HIV, and thus early studies emphasized the relationship between CD4 counts and viral loads and PN.<sup>6,9</sup> PN became more problematic in HIV clinics during the era when neurotoxic nucleosides were commonly used,<sup>3,21</sup> and current clinics continue to follow patients who suffered combined HIV and neurotoxic injuries and have persistent neuropathic symptoms. Additionally, metabolic abnormalities in HIV including diabetes and hyperlipidemia may also lead to nerve injury.<sup>22</sup> Neurotoxic chemotherapy or alcohol use, sometimes associated with nutritional deficiencies, may also contribute to the prevalence of PN in HIV clinics. However, looking at patients treated in the current era who never develop severe immunodeficiency predicts a more optimistic future. It should be emphasized that symptomatic PN is the fundamental concern, given its association with functional impairment and disability.<sup>23,24</sup>

In this well-treated population, we show that painful and symptomatic PN is uncommon, and show little sign of increasing prevalence over 8 years of follow-up. While signs compatible with peripheral nerve damage increased slightly over time, we did not have a control group (HIV-negative population) to assess the impacts of aging or other co-morbid conditions. In our rigorously monitored observed cohort with pre-ART evaluations (Figure 1, Panel B), the prevalence of painful and symptomatic PN is rare and does not develop over prolonged observation.

Pre-ART CD4 may predict peripheral nervous system damage and resulting in PN or SPN. Within our large study population, univariable analyses showed pre-ART CD4 to be associated with SPN and numbness, but multivariable analysis reveals only a marginal association between pre-ART CD4 and sensory neuropathy. Based on this, we conclude that HIV infection causes, at most, a very modest clinical nerve damage before advanced immunodeficiency develops. In Figure 2, the vibratory loss, the most reliable sign of nerve injury, appears to show damage with pre-ART CD4 <100 cells which is consistent with earlier observations of nerve damage at very low CD4 counts.<sup>25,26</sup> Our analysis, designed to isolate the impact of early advanced immunodeficiency on later development of neuropathy independent of viral load also supports the impact of advanced immune injury as the critical

factor in manifestations of PN dysfunction. However, even so, with exception to the association between pre-ART CD4 and numbness, all other neuropathic outcomes were not significant in multivariable models.

Our analysis suggests that given current trends in therapy for HIV worldwide which emphasize early treatment with non-neurotoxic cART, SPN is not likely to be a frequent complication. Although it is important to consider other recognized PN risk factors (including poor nutritional status, diabetes, and alcohol, which may contribute to development or exacerbation of SPN), our observations are consistent with the declining importance of painful and symptomatic PN in association with treated HIV infection. However, the risk of PN has been very consistently associated with increasing age, so the impact of the aging HIV population may in some measure blunt the benefits of earlier, non-toxic ARR.<sup>1,3,27,28</sup>

Limitations of this study include its observational nature with the potential for informative (non-random) drop-out/in, self-selection issues in ART and concomitant medication use, and the potential for selection bias since the participants analyzed are those who volunteered and were able to return for follow-up visits. 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. Also, the neurological examinations were performed by non-neurologists who had received training, but for some parts of the assessments, such as distal ankle jerk, reliability is difficult to establish between examiners and may result in imprecision in some observations.

In summary, this analysis of ART-naïve patients starting non-neurotoxic cART showed a low prevalence of symptomatic PN. Lower pre-ART CD4 counts were associated with asymptomatic and also symptomatic PN (numbness) after cART initiation but not when pre-ART CD4 was > 250 cells/μL, providing additional evidence to support early initiation of ART.

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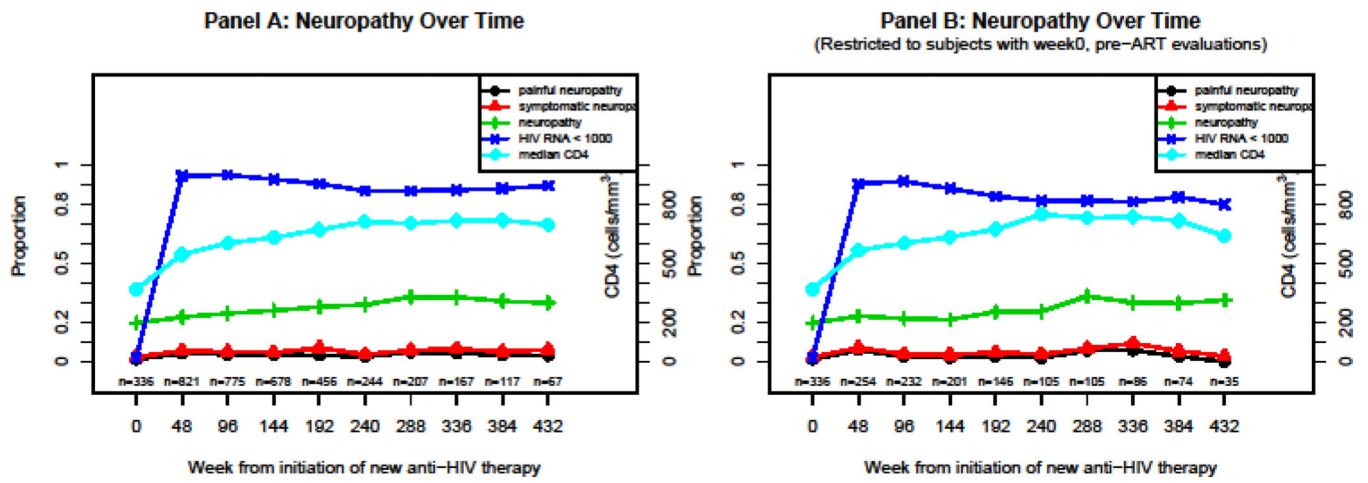


Figure 1. Neuropathy over time

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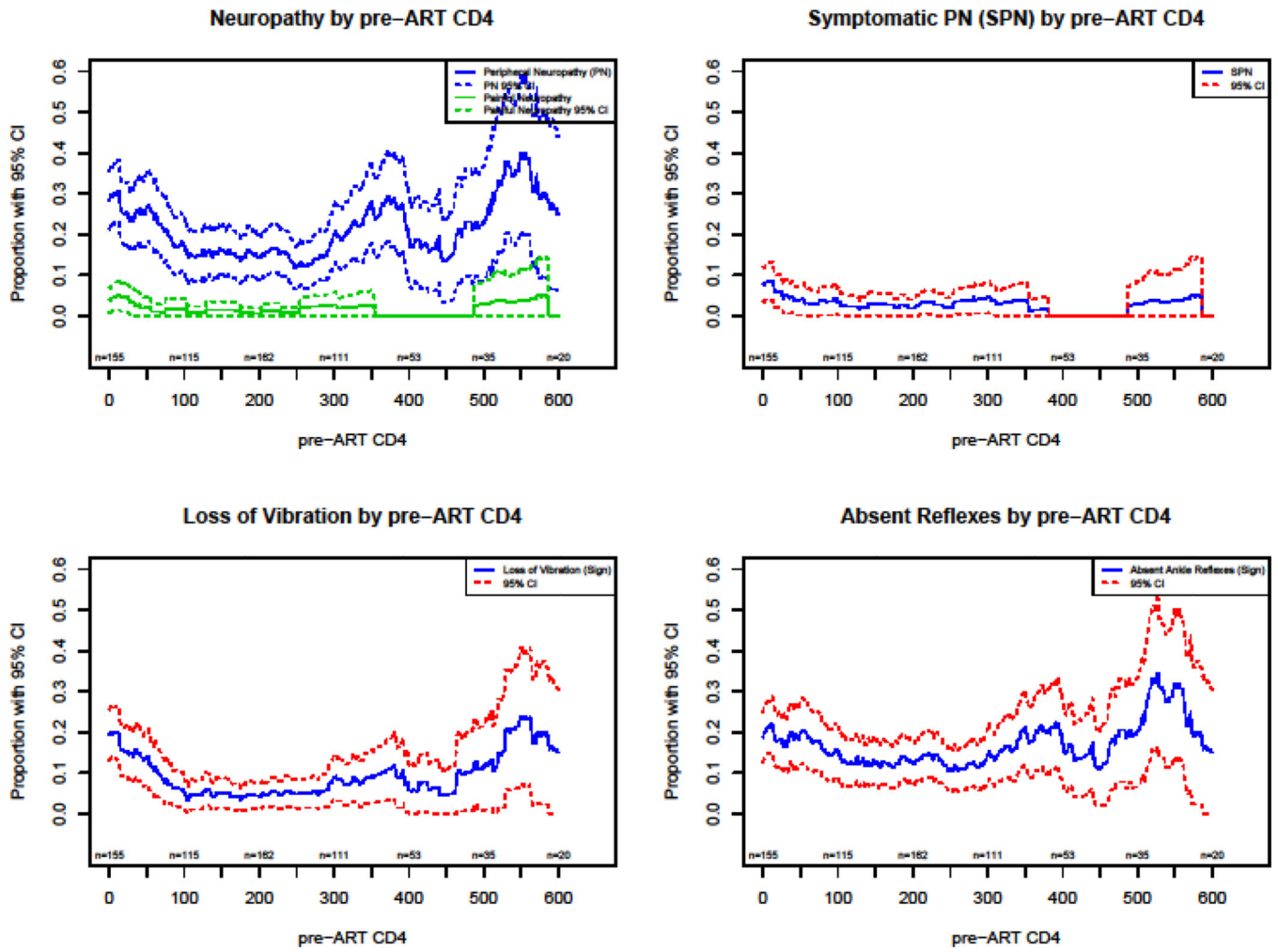
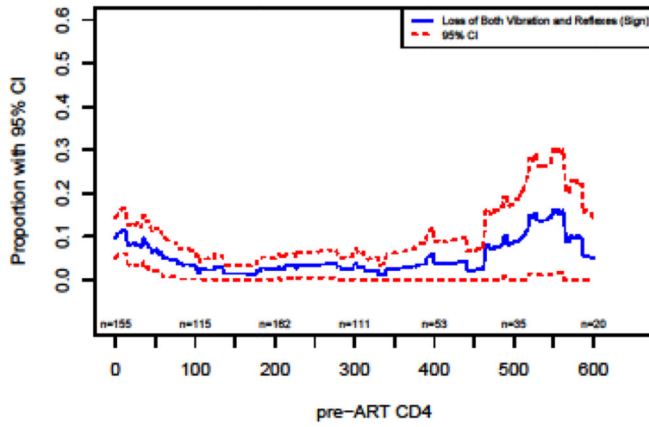
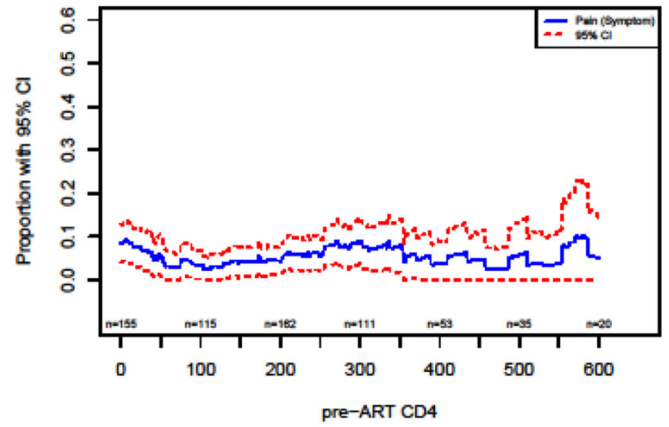


Figure 2.  
Pre-ART neuropathy by pre-ART CD4

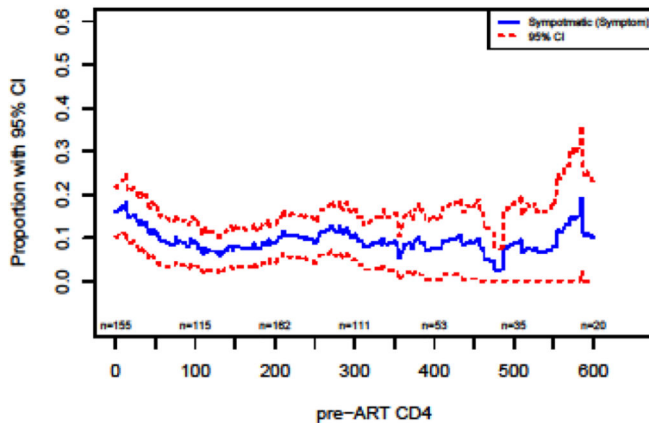
Loss of Vibration and Reflexes by pre-ART CD4



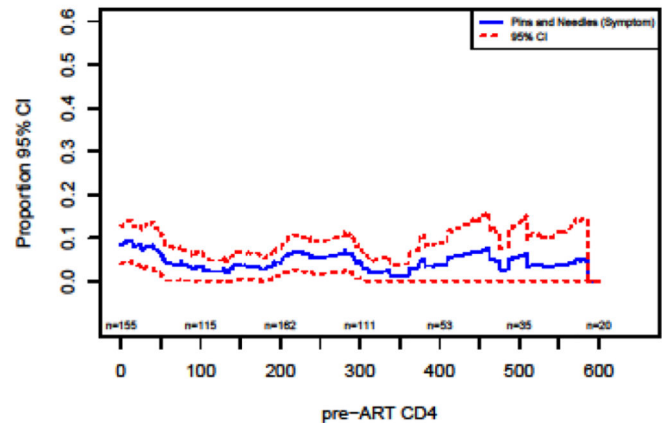
Pain by pre-ART CD4



Symptomatic by pre-ART CD4



Pins and Needles by pre-ART CD4



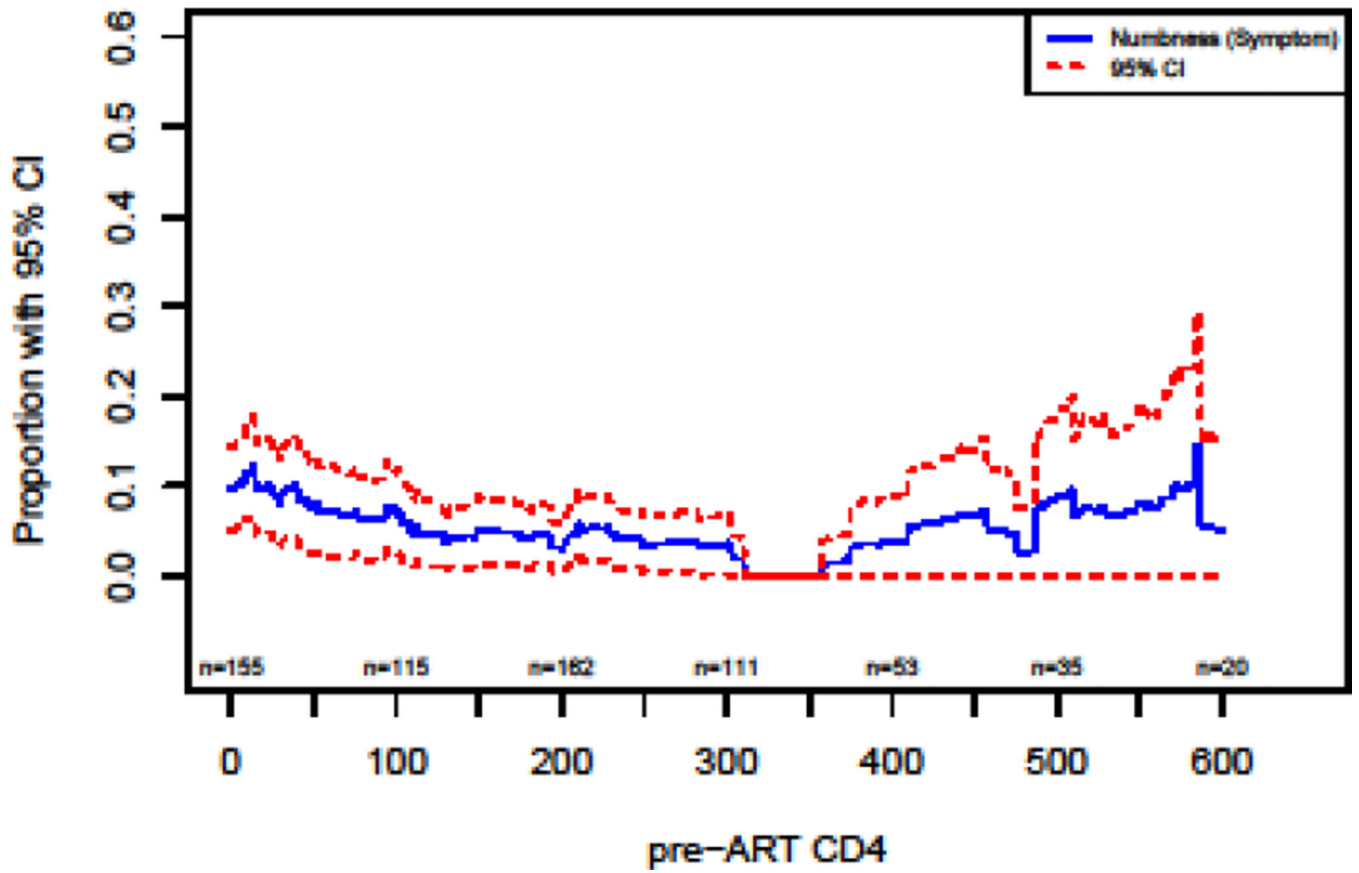
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### Numbness by pre-ART CD4



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Table 1

## Demographics &amp; Baseline Characteristics

Characteristic	Model 1* (N=698)	Model 2† (N=2092)	Model 3‡ (N=1929)	Model 4** (N=996)
Age at Baseline (pre-ART)				
<20	5 (1%)	13 (1%)	10 (1%)	11 (1%)
20-29	125 (18%)	373 (18%)	340 (18%)	207 (21%)
30-39	293 (42%)	787 (38%)	720 (37%)	388 (39%)
40-49	198 (28%)	653 (31%)	609 (32%)	280 (28%)
50-59	67 (10%)	227 (11%)	212 (11%)	97 (10%)
Over 60	10 (1%)	39 (2%)	38 (2%)	13 (1%)
Sex				
Male	598 (86%)	1,713 (82%)	1,579 (82%)	832 (84%)
Female	100 (14%)	379 (18%)	350 (18%)	164 (16%)
Race/Ethnicity				
White	321 (46%)	899 (43%)	852 (44%)	482 (48%)
Black	207 (30%)	685 (33%)	602 (31%)	273 (27%)
Hispanic	150 (21%)	443 (21%)	412 (21%)	206 (21%)
Asian	11 (2%)	40 (2%)	38 (2%)	24 (2%)
Native Indian/Alaskan	4 (1%)	9 (0%)	9 (0%)	3 (0%)
Other	5 (1%)	11 (1%)	11 (1%)	6 (1%)
Unknown/missing	0 (0%)	5 (0%)	5 (0%)	2 (0%)
IV drug history				
No	637 (91%)	1,905 (91%)	1,757 (91%)	904 (91%)
Yes	61 (9%)	187 (9%)	172 (9%)	92 (9%)
HCV seropositivity				
Positive ever	79 (11%)	209 (10%)	190 (10%)	89 (9%)
Negative	597 (86%)	1,883 (90%)	1,739 (90%)	896 (90%)
Not available	22 (3%)	0 (0%)	0 (0%)	11 (1%)
Baseline (pre-ART) CD4 Count (cells/ul)				
N	698	2,092	1,929	996
Median	238	226	229	350
Q1, Q3	109, 362	89, 335	94, 335	299, 440
Baseline (pre-ART) Log <sub>10</sub> (HIV RNA Viral Load),(cp/ml)				
N	698	2,092	1,929	996
Median	4.70	4.68	4.68	4.52
Q1, Q3	4.34, 5.20	4.36, 5.15	4.36, 5.13	4.15, 4.80

\* Model 1: Multivariable logistic regression model used to estimate association between pre-ART CD4 (full range) and neuropathy outcome

Model 2: Multivariable logistic GEE model used to estimate association between pre-ART CD4 (full range) and neuropathy outcome

Model 3: Same as Model 2 but restricted to sub-population (HIV-RNA VL < 50cp/ml)

Model 4: ART-naïve subjects with pre-ART CD4 > 250 cells/ $\mu$ L

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**Table 2**

Association between neuropathy outcomes and full range pre-ART CD4 counts

Association between neuropathy outcomes and pre-ART CD4 (per 100 higher cells/ $\mu$ L)						
Univariable Logistic Regression GEE Models						
Dependent Variable:	At Baseline (pre-ART)		Post-Baseline (post-ART)		Post-Baseline (post-ART), HIV-RNA VL	
	Odds Ratio (95%CI)	p-value	Odds Ratio (95%CI)	p-value	Odds Ratio (95%CI)	p-value
PN	0.99 (0.90, 1.09)	0.85	0.93 (0.89, 0.98)	0.01	0.94 (0.88, 0.99)	0.01
SPN	0.69 (0.52, 0.91)	0.01	0.94 (0.86, 1.02)	0.13	0.93 (0.85, 1.02)	0.13
Painful neuropathy	0.75 (0.52, 1.08)	0.12	0.95 (0.85, 1.05)	0.29	0.95 (0.85, 1.06)	0.33
Loss of vibration (Sign)	0.90 (0.79, 1.04)	0.15	0.92 (0.87, 0.97)	0.003	0.91 (0.85, 0.97)	0.002
Absent reflexes (Sign)	1.01 (0.91, 1.12)	0.85	0.94 (0.88, 0.99)	0.02	0.94 (0.88, 1.00)	0.04
Loss of vibration and reflexes (Sign)	0.88 (0.72, 1.07)	0.19	0.89 (0.82, 0.97)	0.003	0.86 (0.79, 0.95)	<.001
Pain (Symptom)	0.94 (0.80, 1.12)	0.50	0.98 (0.91, 1.05)	0.57	0.98 (0.90, 1.06)	0.62
Symptomatic (Symptom)	0.88 (0.77, 1.01)	0.07	0.97 (0.91, 1.03)	0.30	0.97 (0.91, 1.03)	0.31
Pins and needles (Symptom)	0.83 (0.67, 1.02)	0.07	0.98 (0.91, 1.06)	0.62	0.97 (0.89, 1.05)	0.39
Numbness (Symptom)	0.80 (0.65, 0.98)	0.03	0.92 (0.84, 0.99)	0.03	0.91 (0.83, 0.99)	0.02
Multivariable Logistic Regression GEE Models						
Dependent Variable:	At Baseline (pre-ART)		Post-Baseline (post-ART)		Post-Baseline (post-ART), HIV-RNA VL	
	Odds Ratio (95%CI)	p-value	Odds Ratio (95%CI)	p-value	Odds Ratio (95%CI)	p-value
PN	1.03 (0.93, 1.14)	0.58	0.98 (0.92, 1.04)	0.49	0.99 (0.93, 1.06)	0.82
SPN	0.75 (0.55, 1.03)	0.08	0.97 (0.88, 1.07)	0.59	0.98 (0.89, 1.09)	0.76
Painful neuropathy	0.84 (0.57, 1.25)	0.39	0.93 (0.83, 1.04)	0.18	0.94 (0.83, 1.06)	0.31
Loss of vibration (Sign)	0.98 (0.85, 1.13)	0.78	0.95 (0.88, 1.02)	0.15	0.95 (0.88, 1.03)	0.19
Absent reflexes (Sign)	1.05 (0.93, 1.17)	0.44	0.99 (0.92, 1.07)	0.83	1.00 (0.93, 1.08)	0.95
Loss of vibration and reflexes (Sign)	0.97 (0.79, 1.19)	0.80	0.96 (0.87, 1.05)	0.35	0.94 (0.85, 1.04)	0.23
Pain (Symptom)	1.07 (0.90, 1.27)	0.48	0.98 (0.90, 1.06)	0.62	0.99 (0.90, 1.09)	0.85
Symptomatic (Symptom)	0.96 (0.83, 1.11)	0.58	0.99 (0.93, 1.07)	0.85	1.00 (0.93, 1.08)	0.99
Pins and needles (Symptom)	0.89 (0.70, 1.12)	0.31	0.98 (0.90, 1.08)	0.74	0.97 (0.88, 1.07)	0.56
Numbness (Symptom)	0.84 (0.67, 1.05)	0.13	0.91 (0.83, 1.00)	0.054	0.90 (0.81, 1.00)	0.049



**Table 3**

Prevalence of PN and SPN (restricted to pre-ART CD4 > 250 cells/ul)

Week since cART initiation	PN		SPN		SPN among those with PN	
	N	Neuropathy % (95%CI)	N	Neuropathy % (95%CI)	N	Neuropathy % (95%CI)
0	336	19.6 (15.5, 24.3)	336	2.4 (1.0, 4.6)	66	12.1 (5.4, 22.5)
48	821	22.7 (19.8, 25.7)	821	5.6 (4.1, 7.4)	186	24.7 (18.7, 31.6)
96	775	24.6 (21.6, 27.8)	775	5.0 (3.6, 6.8)	191	20.4 (14.9, 26.8)
144	678	26.0 (22.7, 29.4)	678	4.7 (3.3, 6.6)	176	18.2 (12.8, 24.7)
192	456	27.9 (23.8, 32.2)	456	7.0 (4.8, 9.8)	127	25.2 (17.9, 33.7)
240	244	29.1 (23.5, 35.2)	244	3.7 (1.7, 6.9)	71	12.7 (6.0, 22.7)
288	207	32.9 (26.5, 39.7)	207	5.8 (3.0, 9.9)	68	17.6 (9.5, 28.8)
336	167	32.9 (25.9, 40.6)	167	6.6 (3.3, 11.5)	55	20.0 (10.4, 33.0)
384	117	30.8 (22.6, 40.0)	117	5.1 (1.9, 10.8)	36	16.7 (6.4, 32.8)
432	67	29.9 (19.3, 42.3)	67	6.0 (1.7, 14.6)	20	20.0 (5.7, 43.7)