Peripheral Neuropathy in Primary HIV Infection Associates With Systemic and Central Nervous System Immune Activation

Samantha X.Y. Wang, BA,* Emily L. Ho, MD, PhD,† Marie Grill, MD,‡ Evelyn Lee, BA,* Julia Peterson, BS,‡ Kevin Robertson, PhD,§ Dietmar Fuchs, PhD,|| Elizabeth Sinclair, PhD,‡† Richard W. Price, MD,‡ and Serena Spudich, MD*

Background: Peripheral neuropathy (PN) is a frequent complication of chronic HIV infection. We prospectively studied individuals with primary HIV infection (<1 year after transmission) to assess the presence of and laboratory associations with PN in this early stage.

Methods: Standardized examination and analysis of blood and cerebrospinal fluid (CSF) was performed in participants with laboratory-confirmed primary HIV infection. PN was defined as ≥1 of the following unilateral or bilateral signs: decreased distal limb position, vibration, or temperature sense or hyporeflexia; symptomatic PN (SPN) was defined as the presence of these signs with symptoms. Analysis used nonparametric statistics.

Results: Overall, 20 (35%) of 58 antiretroviral-naive male subjects without diabetes evaluated at a median of 107 days post HIV transmission met criteria for PN. Thirteen (65%) of 20 PN subjects met criteria for SPN; 6 (30%) of 20 had bilateral findings. PN subjects and no PN subjects (NPN) did not differ in median age, days post HIV transmission, blood CD4 or CD8 counts, CSF or plasma HIV RNA levels, CSF white blood cell counts, or CSF to blood albumin ratio. PN and SPN subjects had elevated CSF neopterin (P

Conclusions: Signs of PN were detected by detailed neurologic examination in 35% of men enrolled in a neurological study at a median of 3.5 months after HIV transmission. PN during this early period may be mediated by systemic and nervous system immune responses to HIV.

Key Words: HIV, peripheral neuropathy, cerebrospinal fluid, immune activation


INTRODUCTION

HIV-1 (HIV) affects both the central nervous system (CNS) and peripheral nervous system (PNS).1,2 Nervous system infection with HIV produces a range of clinical disorders, with peripheral neuropathy (PN) as a frequent neurological complication.3 Although many of the end-stage complications of advanced AIDS and immunosuppression are prevented or ameliorated by the use of potent combination antiretroviral therapy (ART), neurological abnormalities persist as detected by reduced performance on neuropsychological testing,4,5 which may reflect damage to both the CNS and the PNS.2,6 The extent of early PNS dysfunction during primary HIV infection (PHI) is unknown, although understanding the frequency and mechanism of PNS involvement may provide therapeutic approaches to neuroprotection in HIV-infected patients.

A distal sensory polyneuropathy (DSP) is the most common type of PN seen in chronic HIV infection or with neurotoxic ART, presenting with symptoms of distal numbness and paresthesias and signs of absent or decreased deep tendon reflexes.7 The exact pathogenesis of HIV-DSP is unknown. Macrophage activation and proinflammatory cytokines associate with neurological disease development and are implicated in the immunopathogenesis of HIV-DSP.8 Proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, interferon-γ, and interleukin-6, have been detected in the dorsal root ganglia (DRG) of HIV-infected patients, suggesting inflammation-mediated neuronal damage.9,10 However, studies have been limited to patients with AIDS, and a little is known about the inflammatory mediators of HIV-DSP in early infection. Although numerous case reports

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From the *Department of Neurology, Yale University School of Medicine, New Haven, CT; †Department of Neurology, Harborview Medical Center, University of Washington Medical Center, Seattle, WA; ‡Department of Neurology, University of California San Francisco, San Francisco, CA; §Department of Neurology, University of North Carolina, Chapel Hill, NC; and ||Division of Biological Chemistry, Biocenter, Innsbruck Medical University, Austria.
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Correspondence to: Samantha X.Y. Wang, BA, Yale University School of Medicine, 15 York Street, New Haven, CT 06510 (e-mail: xiaoyan.wang@yale.edu).
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have described peripheral nerve abnormalities, including DSP, demyelinating neuropathies, and focal neuritis after initial seroconversion,11–13 systematic data assessing when peripheral nerve abnormalities first develop in recent HIV infection and what underlying pathophysiology causes such damage is lacking.

In the first weeks and months of HIV infection, cerebrospinal fluid (CSF) HIV RNA and intrathecal immune activation can be readily detected in untreated patients.14–16 We hypothesized that PN may be present during PHI and that correlations may exist between levels of infectious and inflammatory biomarkers and signs of PN in this setting. To assess whether specific markers of viral replication and immune activation, including monocyte chemoattractant protein-1 (MCP-1), neopterin, interferon-γ-induced protein-10 (IP-10), and activated CD4+ and CD8+ T lymphocytes in a subset of CSF and whole blood from all participants. The study was approved by the Institutional Review Boards at the University of California, San Francisco (UCSF) and Yale University.

METHODS

Study Participants

Baseline visits from a longitudinal neurological study of PHI, defined as within the first 12 months after HIV transmission, were analyzed. Timing of infection was confirmed by a combination of antibody seroconversion, nucleic acid testing, or less sensitive enzyme immunoassay result.17 Days post HIV transmission (DPT) was defined by estimating infection as 14 days before the onset of seroconversion symptoms or, in those with asymptomatic seroconversion, as the date halfway between the last negative and first positive HIV test.18,19 Subjects were excluded if they had diabetes, thyroid disease, or prior ART exposure. Written informed consent was obtained from all participants. The study was approved by the Institutional Review Boards at the University of California, San Francisco (UCSF) and Yale University.

Clinical Evaluation

Presence of PN was determined through an examination by a neurologist (R.W.P., M.G., E.L.H., or S.S.) and recording of signs and symptoms according to a standardized UCSF Macro Neurologic examination (MacroNeuro) created for the AIDS Clinical Trial Group. PN was defined as the presence of unilateral or bilateral signs of decreased position, vibration, or temperature sense at great toes, or the presence of distal pain or tingling on examination with or without hypeflexia or absent or decreased ankle jerks. Diminished vibration was documented as absent sensation of vibration of a 128-Hz tuning fork over a distal bony joint or a reduction of vibration duration compared with testing on the sternum of the subject to that detected by the examiner. A reduction in "cold" sensation from the flat portion of the tuning fork in the distal limbs compared with face and/or proximal limbs was considered a temperature deficit. Symptomatic PN (SPN) met more stringent criteria of having aforementioned signs and symptoms, including numbness and paresthesias. Information about alcohol use, abuse (determined according to modified “CAGE” questions), and intravenous drug use was ascertained by standardized written inventories. Subjects underwent concurrent general medical, neuropsychological, and laboratory assessments. Neuropsychological testing included dominant hand grooved pegboard, nondominant hand finger tapping, digit symbol test, and timed gait. Neuropsychological test Z-scores (NPZ) were calculated for each test using age-adjusted norms and were averaged to a summary NPZ-4 score.

Specimen Sampling and Processing

Laboratory assessments included blood testing and lumbar puncture. CSF total white blood cell, protein, albumin, blood albumin, CD4+ and CD8+ counts by flow cytometry were measured on fresh samples. Cell-free CSF and blood plasma were also aliquoted and stored within 6 hours of collection in −70°C freezers monitored daily for temperature using National Institute of Science and Technology-certified thermometers.

Measurement of Soluble Immune Activation

Concentrations of CSF and blood neopterin, IP-10, and MCP-1 were measured in previously frozen samples at UCSF or in the laboratory of Dr. Fuchs by commercial immunoassays (BRAHMS Aktiengesellschaft, Hennigsdorf, Germany).

Measurement of Cellular Immune Activation

Multiparameter flow cytometry was used to measure the percentage of CD38 and HLA-DR double-positive CD8+ and CD4+ T lymphocytes in a subset of CSF and whole blood samples using previously described methods.20,21 Lymphocyte activation antibody-dye panels were switched halfway through the study, although the 2 panels were compared in analysis and confirmed to have consistent T-lymphocyte activation measures. A further subset of samples was analyzed by flow cytometry for monocyte activation, identifying CD3-negative cells with a CD14+CD16+ phenotype. Blood samples were stained with fluorescence minus one controls in which 1 antibody was omitted. An unstained control and single-stained samples were also prepared as compensation controls. Samples were run on a FACS DIVA (BD Biosciences, San Jose, CA) and analyzed with FlowJo (TreeStar, Ashland, OR).

Virological Methods

HIV RNA levels were measured in previously frozen cell-free CSF and plasma using the ultrasensitive (50 copies/mL lower limit of detection) Amplicor HIV Monitor (version 1.5; Roche Molecular Diagnostic Systems, Branchburg, NJ) or the Abbott RealTime HIV-1 (Abbott Laboratories, Abbott Park, IL) assays. Paired blood and CSF measurements were made using the same assay, in the same polymerase chain reaction run.

Statistical Analysis

Descriptive statistics were performed using Stata/SE 11.0 (StataCorp LP, College Station, TX). Nonparametric
Mann–Whitney rank sum test compared group differences between PN and no PN (NPN), and subgroup differences between SPN and NPN. Fisher exact test compared differences between categorical variables. A regression model compared group differences after adjusting for age, alcohol abuse, and race.

RESULTS

Study Participant Characteristics

Clinical and laboratory characteristics of study subjects are presented in Table 1. Subjects were previously healthy men with a median age of 36 years and CD4⁺ T-cell count of 575 cells per microliter evaluated at a median estimate of 107 DPT. Subjects had normal basal metabolic indices and showed no evidence of nutritional deficiency. Additional demographic data including ethnicity, history of intravenous drug use, alcohol use, and hepatitis C infection status are presented in Table 1.

Clinical and Demographic Associations With PN in Primary Infection

Twenty (35%) of 58 PHI subjects had signs of PN (designated “PN subjects”) upon neurological examination. There was a trend toward PN subjects being older with a median age of 40 years compared with 34 years in subjects with NPN ($P = 0.05$). There was no significant relationship between history of alcohol abuse and signs of PN ($P = 0.05$). Of the 20 PN subjects, 6 subjects had bilateral findings, 7 had unilateral findings, and in the remaining 7 subjects, laterality was not specified. Neuropsychological performance was not different between the PN and NPN groups (PNZ-4, −0.24, interquartile range (IQR), −0.70 to 0.22 vs. NPZ-4, 0.02; IQR, −0.50 to 0.65; $P = 0.18$). There was no difference in DPT between the 2 groups. The PN group showed no significant difference compared with the PN group in absolute blood CD4⁺ (582 cells/μL; IQR, 408–729 vs. 558 cells/μL; IQR, 453–715; $P = 0.82$) and CD8⁺ T-cell counts (1019 cells/μL; IQR, 674–1543 vs. 901 cells/μL; IQR, 701–1202; $P = 0.59$).

Thirteen of the 20 PN subjects (65% of PN and 22% of total) also had symptoms of PN (SPN). Typical symptoms included “foot tingling and numbness.” There were no demographic differences identified between NPN and SPN subjects.

Laboratory Associations With PN in Primary Infection

Median plasma HIV RNA levels and CSF HIV RNA levels were similar between PN and NPN groups and between

| TABLE 1. Clinical and Demographic Characteristics of Study Participants by Group |
|------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                        | Overall Median | NPN             | PN              | SPN             | $P$             |
| Number                 | 38             | 20              | 13              |                 |                 |
| Age (yr)               | 36             | 34 (27–42)      | 40 (31–47)      | 37              | 0.05*           |
| Years of education     | 16             | 16              | 15              | 14              | 0.13*           |
| Days post-HIV transmission | 107          | 104 (65–188)   | 125 (74–164)    | 137 (72–172)    | 0.87*           |
| CD4⁺ T-cell count (cells/μL) | 575          | 558 (408–729)  | 582 (453–715)   | 601 (483–755)   | 0.83*           |
| CD8⁺ T-cell count (cells/μL) | 985          | 701 (513–1202) | 1019 (674–1543) | 1053 (736–1635) | 0.59*           |
| Plasma HIV RNA (log₁₀ copies/mL) | 4.45        | 4.37 (3.94–4.77) | 4.79 (3.17–5.18) | 4.82 (3.00–5.28) | 0.29*           |
| Race/ethnicity         |                |                 |                 |                 |                 |
| White, n (%)           | 29 (49.2)      | 10 (17.2)       | 8 (13.8)        | 0.08*           |
| History of intravenous drug use |            |                 |                 |                 | 0.35†           |
| Yes, n (%)             | 27 (46.6)      | 16 (27.6)       | 10 (17.2)       | 0.72*           |
| History of alcohol use, n (%) |            |                 |                 |                 | 0.52†           |
| Yes                    | 12 (20.7)      | 13 (22.4)       | 8 (13.8)        | 0.05*           |
| Unknown                | 3 (7.9)        | 0 (0)           | 0 (0)           | 0.65†           |
| Hepatitis C infection status, n (%) |            |                 |                 |                 |                 |
| Yes                    | 1 (2.6)        | 0 (0)           | 0 (0)           | —               |
| Unknown                | 5 (13.2)       | 0 (0)           | 0 (0)           | —               |

Values are presented as medians (IQR) unless otherwise noted.

* NPN vs. PN.
† SPN vs. PN.
SPN and NPN groups. CSF white blood cell count (8.00 cells/μL; IQR, 2.00–10.00 vs. 6.00 cells/μL; IQR, 2.00–12.00; P = 0.48) and albumin ratios (4.96; IQR, 4.46–6.53 vs. 5.47; IQR, 4.23–8.25; P = 0.76) were similar between PN and NPN subjects. Median levels of blood neopterin (17.9 nmol/L; IQR, 15.4–25.3 vs. 12.1 nmol/L; IQR, 8.8–20.0; P = 0.006), CSF neopterin (13.7 nmol/L; IQR, 8.0–21.9 vs. 8.1 nmol/L; IQR, 5.2–9.5; P = 0.003), CSF MCP-1 (620 pg/mL; IQR, 534–780 vs. 477 pg/mL; IQR, 373–643; P = 0.006), and IP-10 (910 pg/mL; IQR, 401–1749 vs. 530 pg/mL; IQR, 323–907; P = 0.09) in the PN subjects were elevated as compared with the NPN subjects (Figs. 1A–E).

Additional analysis adjusted for age, alcohol use, and race showed continued significant elevation of CSF neopterin (P = 0.02) and blood neopterin (P = 0.008) in PN compared with NPN subjects. There remained a trend for MCP-1 to be elevated in PN subjects, but the association was not statistically significant (P = 0.05).

Flow cytometric analysis of CD8+ T-lymphocyte activation revealed similar median percentage of activated CD38+/HLA-DR+ CD8+ T lymphocytes in PN subjects in blood (P = 0.23) but an elevated percentage in the CSF compartment (77.6%; IQR, 69.4–86.8 vs. 60.9%; IQR, 49.7–68.0; P = 0.004; Figs. 2A–D) compared with NPN subjects. There were no differences in percentages of activated CD4+ T lymphocytes or activated CD14+CD16+ monocytes in blood or CSF between PN and NPN.

When PN only subjects were excluded from the analysis, and CSF and blood samples for inflammatory biomarkers were compared between SPN and NPN subjects, elevated levels of CSF neopterin (14.3 nmol/L; IQR, 5.9–29.7 vs. 8.1 nmol/L; IQR, 4.4–9.5; P = 0.005), CSF MCP-1 (623 pg/mL; IQR, 330–791 vs. 477 pg/mL; IQR, 208–643; P = 0.01), CSF IP-10 (1063 pg/mL; IQR, 432–2242, vs. 530 pg/mL; IQR, 327–907; P = 0.03), and blood neopterin (17.7 nmol/L; IQR, 10.8–32.4 vs. 12.1 nmol/L; IQR, 4.3–12.1; P = 0.009) were found in the SPN group. Percentage of activated CD4+ T lymphocytes and monocytes did not differ between the SPN and PN subjects in either compartment.

**DISCUSSION**

PN is a frequent neurological disorder reported in HIV, classically in the setting of chronic untreated HIV infection or after exposure to certain antiretroviral medications. However, we found that signs (35%), or signs and symptoms (22%), of PN were evident in a cohort of ART-naïve subjects recruited to a neurological study at a median of 3.5 months after initial
HIV transmission. We further examined mechanisms for peripheral nerve dysfunction identified during this stage, revealing that markers of systemic and CNS immune activation are elevated in subjects with signs of neuropathy (PN) compared with those with no signs of neuropathy (NPN).

Disorders of the PNS manifesting during PHI, typically around the period of HIV seroconversion, are well-described in case reports and series, and include acute inflammatory demyelinating peripheral neuropathies, meningoencephalitis, and ataxic neuropathy. However, subtle signs and symptoms of PN during PHI have not been systematically studied. The pathogenesis of classic HIV-DSP is not clearly elucidated, but it is thought to be due to a combination of direct viral toxicity and immune activation. Increased monocyte–macrophage markers, lymphocyte and macrophage infiltration, and cytokine expression are detected in the peripheral nerves and DRGs of patients with DSP in AIDS, with resulting distal demyelination and axonal degeneration in a “dying back” pattern. The immunologic response to HIV begins in early disease with chemokine elevation, including MCP-1 and IP-10, and the macrophage activation marker neopterin, in the blood and CSF of HIV patients with normal CD4+ T-cell counts and even during PHI.

We found high rates of PN in our cohort of PHI subjects. As subjects with symptomatic seroconversion and neurologic symptoms may have been more likely to enroll in the study, it is possible that the prevalence of PN in our cohort is higher than in all individuals with PHI. This may be one contributing factor to differences between our findings and that of a previous study, which observed a much lower rate of HIV-associated PN in chronic infection. Additionally, HIV transcripts and proteins have been detected in DRG neurons and surrounding satellite cells in subjects with PN and HIV-DSP. However, it is generally believed that HIV replication in peripheral nerves is scarce. CSF HIV RNA, CSF total protein levels [a measurement of all detected CSF proteins indicative of blood–brain barrier (BBB) integrity], and CSF to blood albumin ratios (a highly specific marker of BBB integrity) were similar between PN and NPN subjects, suggesting that the viral burden measurable within the nervous system and BBB penetrance may not contribute to neuropathy during PHI.

Amplified immune activation characterized our subjects with signs of PN. CSF markers have been previously

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implicated in advanced stages of HIV neurological disease progression: CSF neopterin increases along with CNS HIV disease severity and decreases following ART\textsuperscript{31}; levels of IP-10 positively correlate with the presence of HIV-associated dementia (HAD)\textsuperscript{32}; elevated MCP-1 is detected in the brain and CSF of subjects with HIV encephalitis and HAD.\textsuperscript{33,34} Our results support the premise that immune activation is crucial to peripheral neurological dysfunction in HIV. The chemokreceptor MCP-1 and IP-10 likely escalate disease through augmentation of viral replication in already-infected cells and enhance local inflammation by lymphocyte and monocyte recruitment.\textsuperscript{35,36} With increased monocyte activation and macrophage presence, HIV cellular transmission perpetuates, and infection leads to macrophage priming and induction of proinflammatory cytokines and TNF-\alpha, leading to neuronal dysfunction. Furthermore, in rat models, endothelial cells that supply DRGs are highly fenestrated, suggesting that this area of the PNS may be particularly vulnerable to toxic effects of circulating activated monocytes and proinflammatory cytokines.\textsuperscript{37}

Our findings of increased CNS inflammation in the presence of PN may be explained through alternative models: HIV concurrently infects both the CNS and PNS, and our detected associations are coincidental, or alternatively, PN induces secondary changes within the CNS. In support of the former, studies of simian immunodeficiency virus-infected macaques at 12 weeks post inoculation have detected increased monocyte infiltration of DRGs and decreased DRG neuronal density and conduction velocity in the absence of neuritis or damage to myelinated peripheral nerves.\textsuperscript{38} Thus, although there may be an association between central and peripheral immune activation, the presence of CNS and PNS lesions may not correlate. Alternatively, in HIV-DSP, macrophage secretion of proinflammatory molecules within the nerve may lead to CNS immune activation. In support of this, perineurial application of the HIV envelope glycoprotein gp120 to rat sciatic nerves leads to TNF-\alpha expression in the DRG and glial cells in the spinal cord.\textsuperscript{39} Proinflammatory cytokines may promote a paracellular route for HIV-1 across the BBB, facilitating HIV infection of the CNS.\textsuperscript{40} MCP-1 contributes to blood–spinal cord barrier permeability after peripheral nerve injury, and individuals with mutant MCP-1 genotypes have an increased risk of HAD and accelerated disease progression.\textsuperscript{41,42} Therefore, a cycle of immune activation and subsequent overproduction of proinflammatory cytokines and chemokines may allow for further cell trafficking from the periphery into the CNS to create further inflammation and neuronal damage.

In our participants, flow cytometry analysis of T-lymphocyte activation demonstrated elevated percentages of CD38\textsuperscript{+}/HLA-DR\textsuperscript{+} CD8\textsuperscript{+} T lymphocytes in the CSF of PN subjects. HLA-DR and CD38 expression on CD8\textsuperscript{+} T lymphocytes correlates with clinical stages of HIV disease, with simultaneous expression of both increasing in symptomatic disease.\textsuperscript{43} MHC class II molecule HLA-DR expression increases in CD8\textsuperscript{+} T lymphocytes upon HIV seroconversion and remains stable, whereas the expression of CD38 levels on CD8\textsuperscript{+} lymphocytes increases throughout disease and is thought to be a predictor of AIDS progression and death.\textsuperscript{44,45} The percentage of CD38\textsuperscript{+} and HLA-DR\textsuperscript{+} CD8\textsuperscript{+} T lymphocytes increases progressively with advancing HIV disease in pre-ART subjects,\textsuperscript{46} although ART decreases the level of blood CD38\textsuperscript{+}/HLA-DR\textsuperscript{+} coexpression on CD8\textsuperscript{+} T lymphocytes, even in subjects only partially responsive to treatment.\textsuperscript{47} Our findings suggest that increased migration to or accumulation of “activated” phenotype CD8\textsuperscript{+} T lymphocytes within the CSF pathologically associates with PN. This is the first study to examine T-lymphocyte activation in the CNS compartment in relation to clinical neurological disease in HIV. Whether these findings indicate that PN is associated with processes accelerating disease progression within the nervous system or another mechanism of injury warrants further study.

We examined the PN group using more stringent criteria of both signs and symptoms of PN, identifying 13 SPN subjects. When compared with our NPN group, elevations in inflammatory markers of CSF neopterin, CSF MCP-1, CSF IP-10, and blood neopterin were noted. The lack of association between the presence of SPN and monocyte and T-lymphocyte activation levels could be due to lower samples in this subgroup, reducing our power to detect significant differences from NPN. The consistency in the elevation of inflammatory markers in the setting of symptomatic disease supports the explanation that PN is mediated in part by an inflammatory response. Animal studies have demonstrated elevated proinflammatory cytokines in rats experiencing sustained allodynia and hyperalgesia following intrathecal and perineural gp-120 administration, which is thought to be neurotoxic and lowers the excitation threshold.\textsuperscript{48,49} This aberrant immune response may lead to neuronal hyperexcitability, creating exaggerated pain states that explain symptomatic PN seen in early infection.

Limitations of this study include the cohort homogeneity because all subjects were ART-naïve men who have sex with men with PHI, within a focused range of age and education. Although this limits generalizability, it allows for the examination of the effects of early HIV with reduced confounders, such as potential toxicities of ART. Furthermore, although we did not perform electromyography and nerve conduction studies in our subjects to electrophysiologically characterize neuropathy, our diagnostic criteria have been used previously in studies examining HIV-PN.\textsuperscript{29,51} Importantly, potential confounders to the analysis need to be considered, and the PN subjects had elevated rates of alcohol abuse compared with NPN subjects. Previous studies have shown that age,\textsuperscript{3} alcohol abuse,\textsuperscript{53} and ethnicity\textsuperscript{24} are risk factors for PN. Our adjusted analyses suggest that although these factors may contribute to and be confounders to the finding of PN, in the context of elevated CNS and systemic immune activation, they are unlikely to entirely explain our finding of a notable relationship between immune activation and the presence of PN. PN may also develop in the setting of nutritional deficiencies.\textsuperscript{55} Although we did not measure vitamin levels in subjects, none had advanced HIV infection, food insecurity, signs of wasting, or low basal metabolic indices. Thus, the presence of vitamin deficiency contributing to nutritional neuropathy seems doubtful. Finally, the results of this study are limited to the timeframe of PHI. Longitudinal follow-up of our cohort is underway to study the natural history of PN in early infection and to investigate...
whether neuropathy during early infection is transient or progressive.

Previous studies have examined the prevalence of PN in HIV-infected individuals on ART, in subjects with long-standing, chronic HIV infection, or AIDS. This is the first study to examine the prevalence of PN among ART-naive individuals within the first months after HIV acquisition. We found a high rate of PN among PHI subjects that correlated with an increased levels of systemic and intrathecal proinflammatory markers. Recognition of PHI as an essential period of immune activation associated with PN and neurological disorders may provide rationale for more aggressive screening for recent HIV infection, and early institution of ART and possibly immunomodulatory therapy during this early period.

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