Continued High Prevalence and Adverse Clinical Impact of Human Immunodeficiency Virus–Associated Sensory Neuropathy in the Era of Combination Antiretroviral Therapy

The CHARTER Study

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Objective: To provide updated estimates of the prevalence and clinical impact of human immunodeficiency virus–associated sensory neuropathy (HIV-SN) and neuropathic pain due to HIV-SN in the combination antiretroviral therapy (CART) era.

Design: Prospective, cross-sectional analysis. Clinical correlates for HIV-SN and neuropathic pain, including age, exposure to CART, CD4 levels, plasma viral load, hepatitis C virus infection, and alcohol use disorders, were evaluated in univariate and multivariate models.

Setting: Six US academic medical centers.

Patients: One thousand five hundred thirty-nine HIV-infected individuals enrolled in the CNS (Central Nervous System) HIV Anti-Retroviral Therapy Effects Research study.

Main Outcome Measures: The presence of HIV-SN, defined by 1 or more clinical signs (diminished vibration or sharp sensation in the legs and feet; reduced ankle reflexes) in a distal, symmetrical pattern. Neuropathic pain was defined as aching, stabbing, or burning in a similar distribution. The effect on quality of life was assessed with the Medical Outcomes Study HIV Health Survey.

Results: We found HIV-SN in 881 participants. Of these, 38.0% reported neuropathic pain. Neuropathic pain was significantly associated with disability in daily activities, unemployment, and reduced quality of life. Risk factors for HIV-SN after adjustment were advancing age (odds ratio, 2.1 [95% confidence interval, 1.8-2.5] per 10 years), lower CD4 nadir (1.2 [1.1-1.2] per 100-cell decrease), current CART use (1.6 [1.3-2.8]), and past “D-drug” use (specific dideoxynucleoside analogue antiretrovirals) (2.0 [1.3-2.6]). Risk factors for neuropathic pain were past D-drug use and higher CD4 nadir.

Conclusions: Neuropathic pain and HIV-SN remain prevalent, causing substantial disability and reduced quality of life even with successful CART. The clinical correlates of HIV-SN have changed with the evolution of treatment. These findings argue for redoubled efforts to determine HIV-SN pathogenesis and the development of symptomatic and neuroregenerative therapies.

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SINCE THE WIDESPREAD introduction of combination antiretroviral therapy (CART) in 1996, many neurological complications of human immunodeficiency virus (HIV) infection have declined, but the effect on peripheral nervous system disease is less clear. Human immunodeficiency virus is most commonly associated with a predominantly sensory polyneuropathy due to viral infection per se or due to a toxic neuropathy associated with specific dideoxynucleoside analogue antiretrovirals (stavudine, didanosine, and zalcitabine; ie, the “D drugs”). Although differing in etiopathogenesis, these disorders are clinically and physiologically similar, making them difficult to distinguish in individual patients. Together they are designated HIV-associated sensory neuropathy (HIV-SN).

Human immunodeficiency virus–associated sensory neuropathy has a seri-
ous effect on patient quality of life, including on sleep and diverse aspects of physical and emotional functioning. Spontaneous pain is common, and clinicians and patients report that pain often does not respond fully to the usual analgesic medications. Additional symptoms include paresthesias and sensory loss. Although the recognition that D drugs can be neurotoxic has led providers in developed countries to substitute alternatives, stavudine remains the single most commonly used component of fixed-dose generic drugs being used in the worldwide initiative to treat HIV and AIDS. This makes the study of susceptibility for HIV-SN especially relevant now.

The goal of this study was to provide updated estimates of the prevalence, risk factors, and effect on daily functioning and employment of HIV-SN and neuropathic pain, especially in relation to evolving CART and aging of the HIV population. To identify cases of HIV-SN, we used a research definition previously demonstrated to provide an optimal balance of sensitivity and specificity compared with expert HIV neurologists’ clinical diagnoses. Several considerations guided our selection of potential risk factors for HIV-SN. Previous reports have consistently demonstrated that HIV-SN is more prevalent among older individuals and those with lower CD4 nadirs, a marker of immune compromise. We also evaluated CART itself as a risk factor, including current or past use, and neurotoxic D-drug exposure. We assessed indicators of response to CART, including plasma viral load and recovery of CD4 levels. Because some studies have suggested that hepatitis C virus (HCV) coinfection may contribute to neuropathy, this was also evaluated as a potential risk factor. Finally, we assessed common comorbidities associated with sensory neuropathies, such as history of alcohol dependence or abuse. Because neuropathic pain is not universal, we also sought to delineate factors associated with pain in HIV-SN. Whereas in a previous report we assessed protease inhibitor use as a risk factor, we herein evaluated multiple risk factors and determined the prevalence and impact of neuropathic pain.

**METHODS**

**DESIGN**

The CNS (Central Nervous System) HIV Anti-Retroviral Therapy Effects Research (CHARTER) Study is a prospective, observational study conducted at the following 6 US locations: The Johns Hopkins University, Baltimore, Maryland; Mount Sinai School of Medicine, New York, New York; University of California, San Diego; The University of Texas, Galveston; University of Washington, Seattle; and Washington University, St Louis, Missouri. Institutional review boards at each site approved this research, and each participant gave informed consent. This cross-sectional analysis included 1539 HIV-infected individuals enrolled between September 1, 2003, and August 31, 2007. Data were collected according to a protocol of comprehensive neuromedical, neurobehavioral, and laboratory assessments that were standardized across sites.

**PARTICIPANTS**

All participants were ambulatory and underwent evaluation in outpatient research centers. Eligibility criteria included the ability to undergo a structured clinical interview to provide details of CART use and a standardized examination for symptoms and signs of HIV-SN. The CHARTER Study inclusion criteria were broad; individuals were excluded only for active opportunistic infections or uncontrolled major psychiatric disorders or for inability to cooperate with a full day of clinical evaluation. Comorbidities such as HCV infection and substance abuse were permitted.

**HIV-SN AND PAIN**

Physicians and nurses trained in neurological AIDS disorders performed a standardized, targeted neurological examination to evaluate HIV-SN signs, including diminished ability to recognize vibration and reduced sharp-dull discrimination in the feet and toes or reduced ankle reflexes. The presence of at least 1 sign bilaterally was considered to be evidence of HIV-SN. For confirmatory analyses, a more stringent criterion of 2 or more signs was used. Neuropathy symptoms also were assessed in the legs, feet, and toes and included bilateral neuropathic pain and dysesthesias (burning, aching, or shooting), paresthesias, and loss of sensation. Using a standardized form and a structured interview, clinicians classified neuropathic pain into the following 5 severity levels: none, slight (occasional, fleeting), mild (frequent), moderate (frequent, disabling), and severe (constant, daily, disabling, requiring analgesic medication or other treatment).

**NEUROMEDICAL, NEUROBEHAVIORAL, AND LABORATORY ASSESSMENTS**

The following clinical correlates and risk factors for HIV-SN and pain were evaluated using structured interviews and laboratory assessments where appropriate: CART use, including current and past exposure to D drugs; HIV disease markers (plasma viral load and CD4 nadir); CD4 recovery level during CART; and HCV serology. Blood was collected by means of venipuncture and used to quantify plasma HIV viral loads by reverse transcription polymerase chain reaction ultrasensitive assay (nominal lower quantitation limit, 50 copies/mL [Amplicor, Roche Diagnostic Systems, Indianapolis, Indiana]). Current CD4 levels were measured by means of flow cytometry. Participants were asked to recall their lowest previous (nadir) CD4 level, and immune recovery was calculated as the difference between the nadir and current CD4 levels.

Dependence in instrumental activities of daily living (IADLs) was assessed with a modified version of the Lawton and Brody Scale that asks participants to rate their current and best lifetime levels of independence for 13 major IADLs such as shopping, financial management, transportation, and medication management. An employment questionnaire asked about job loss, decreases in work productivity, accuracy, and quality; increased effort required to do one’s usual job; and increased fatigue with the usual workload.

Psychiatric diagnoses were assessed using the computer-assisted Composite International Diagnostic Interview, a fully structured measure widely used in psychiatric research. The Composite International Diagnostic Interview classified current and lifetime histories of mood disorders (including major depression) and alcohol abuse and dependence disorders. Current mood was assessed by the Beck Depression Inventory II.

The Medical Outcomes Study HIV Health Survey (MOS-HIV) has been shown to be a reliable and valid tool for assessing overall quality of life, daily functioning, and physical health. The MOS-HIV contains 36 questions that assess physical and mental dimensions of health. These are scored as summary percentile scales ranging from 0 to 100, with higher scores indicating better health.
### Table 1. Demographic and Clinical Characteristics of Participants

<table>
<thead>
<tr>
<th>Value</th>
<th>Unadjusted</th>
<th>Adjusted</th>
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<tbody>
<tr>
<td>Age, mean (SD), y&lt;sup&gt;c&lt;/sup&gt;</td>
<td>46.0 (7.8)</td>
<td>40.0 (8.3)</td>
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<tr>
<td>Male, No. (%)</td>
<td>677 (76.8)</td>
<td>500 (76.0)</td>
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<tr>
<td>CART use, No. (%)</td>
<td>711 (80.7)</td>
<td>384 (58.4)</td>
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<tr>
<td>Current</td>
<td>99 (11.2)</td>
<td>111 (16.9)</td>
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<tr>
<td>Past</td>
<td>71 (8.1)</td>
<td>163 (24.8)</td>
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<tr>
<td>D-drug use, No. (%)</td>
<td>138 (15.7)</td>
<td>72 (10.9)</td>
</tr>
<tr>
<td>Current</td>
<td>413 (46.9)</td>
<td>175 (26.6)</td>
</tr>
<tr>
<td>Past</td>
<td>330 (37.5)</td>
<td>411 (62.5)</td>
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<tr>
<td>CD4 nadir, median (IQR), cells/µL&lt;sup&gt;d&lt;/sup&gt;</td>
<td>120 (30-246)</td>
<td>231 (196-338)</td>
</tr>
<tr>
<td>CD4 recovery level, median (IQR), cells/µL&lt;sup&gt;e&lt;/sup&gt;</td>
<td>229 (87-404)</td>
<td>161 (44-317)</td>
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<tr>
<td>Plasma viral load, median (IQR), log&lt;sub&gt;10&lt;/sub&gt; copies/mL</td>
<td>1.9 (1.7-3.7)</td>
<td>2.7 (1.7-4.3)</td>
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<tr>
<td>HCV infection, No. (%)</td>
<td>284 (30.0)</td>
<td>138 (21.0)</td>
</tr>
<tr>
<td>History of alcohol abuse/dependence, No. (%)</td>
<td>494 (56.1)</td>
<td>351 (53.3)</td>
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**OR (95% CI)<sup>b</sup>**

<table>
<thead>
<tr>
<th>Sign of HIV-SN (n=881)</th>
<th>No HIV-SN (n=658)</th>
<th>P Value</th>
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**Abbreviations:** CART, combination antiretroviral therapy; CI, confidence interval; D-drug, dideoxynucleoside analogue antiretroviral; HCV, hepatitis C virus; HIV-SN, human immunodeficiency virus–associated sensory neuropathy; IQR, interquartile range; OR, odds ratio.

<sup>a</sup>Univariate (unadjusted) and multivariate (adjusted) ORs are presented. Percentages have been rounded and might not total 100.

<sup>b</sup>Odds ratios were calculated per 100-cell increase.

<sup>c</sup>Odds ratios were calculated per 10-year increase.

<sup>d</sup>Odds ratios were calculated per 100-cell decrease.

<sup>e</sup>Odds ratios were calculated per 100-cell increase.

### STATISTICAL ANALYSIS

Demographic and clinical differences between those with and without HIV-SN were evaluated in univariate models. The CD4 counts were compared by the Wilcoxon rank sum test, and age, log<sub>10</sub> plasma viral loads, and MOS-HIV scores were compared by t tests. For coding variables with highly skewed or otherwise nonnormal distributions, we used alternative approaches such as categorical analysis, which gave substantially similar results. Continuous variables including age and CD4 recovery were categorized and assessed in univariate logistic regression models to determine unadjusted odds of HIV-SN and pain. Variables significant in the univariate analyses based on the χ<sup>2</sup> test were introduced into a multivariate model. Mixed (forward/backward), stepwise logistic regression was used to determine a final, reduced model that predicted HIV-SN or pain. Variables associated with P < .05 in the adjusted model are reported. All statistical analyses were performed using a commercially available statistical package (JMP, version 7.0; SAS Institute Inc, Cary, North Carolina). Data are expressed as number (percentage), mean (SD), or median (interquartile range [IQR]).

### RESULTS

#### CHARACTERISTICS OF THE STUDY COHORT

Study participants were mostly nonwhite (929 [60.4%]), middle-aged (mean age, 43.2 [8.5] years) men (1178 [76.5%]) with a high school education (mean, 12.5 [2.5] years). Most (967 [62.8%]) met 1993 Centers for Disease Control and Prevention criteria for AIDS. The median nadir and current CD4 levels were 175/µL (49/µL-300/µL) and 419/µL (263/µL-602/µL). CART use was divided among current (1095 [71.2%]), naive (234 [15.2%]), or past (210 [13.6%]). D-drug use was also divided among current (210 [13.6%]), naive (741 [48.1%]), or past (588 [38.2%]). Among participants with current or past D-drug use, the median exposure duration was 36 (13-68) months. Four hundred two individuals (26.1%) were HCV seropositive and 845 (54.9%) had a history of alcohol abuse or dependence.

### PREVALENCE AND RISK FACTORS FOR HIV-SN DEFINED BY ABNORMAL SIGNS ON NEUROLOGICAL EXAMINATION RESULTS

Human immunodeficiency virus–associated sensory neuropathy, defined as the presence of at least 1 abnormal neuropathy sign, was found in 881 participants (57.2%). Table 1 presents univariate and multivariate odds ratios (ORs) for selected HIV-SN risk factors. Compared with participants without HIV-SN, those with 1 or more signs were older (mean age, 46.0 [7.8] vs 40.0 [8.3] years; P < .001, t test); had more frequent current use of CART (711 [80.7%] vs 384 [58.4%]; P < .001, χ<sup>2</sup> test) and more frequent D-drug exposure (551 [62.5%] vs 247 [37.5%]; P < .001); had lower median CD4 nadirs (120/µL [30/µL-246/µL] vs 231/µL [106/µL-367/µL]; P < .001, Wilcoxon rank test), lower median CD4 current levels (407/µL [247/µL-589/µL] vs 429/µL [283/µL-625/µL]; P = .02, Wilcoxon rank test), greater median CD4 level recovery (229/µL [87/µL-404/µL] vs 161/µL [44/µL-317/µL]; P < .001, Wilcoxon rank test), and lower median log<sub>10</sub> plasma viral load (1.9 [1.7-3.7] vs 2.7 [1.7-4.3]; P < .001, Wilcoxon rank test); and were more frequently seropositive for HCV (264 [30.0%] vs 138 [21.0%]; P < .001). In a multivariate model, the following factors were significantly associated with increased odds of HIV-SN after adjusting for other factors: older age, lower CD4 nadir, current CART use, and past D-drug therapy. Among the 607 participants receiving CART with an undetectable plasma viral load, the risk of neuropathy in those with CD4 nadirs of less than 350/µL was higher than for participants with levels of more than 350/µL (356...
of 543 [65.6%] vs 30 of 64 [46.9%]; OR, 2.16 [95% confidence interval (CI), 1.28-3.64]; P = .004). The increased risk of HIV-SN with lower CD4 nadirs remained significant after adjusting for D-drug use, age, and duration of HIV infection. Those with HIV-SN were less likely to be employed (OR, 0.65 [95% CI, 0.52-0.82]; P < .001) and were more dependent in IADLs (1.36 [1.06-1.61]; P = .02).

When we used the more stringent definition of 2 or more signs, 429 of 1539 participants (27.9%) had HIV-SN. Significant risk factors for HIV-SN were similar to the 1-sign criterion. After mixed (forward/backward), stepwise regression, significant independent predictors of HIV-SN were older age, lower CD4 nadir, current CART, and past D-drug therapy.

### PREVALENCE OF NEUROPATHIC PAIN AND OTHER NEUROPATHY SYMPTOMS

Of those with 1 or more abnormal signs, 536 (60.8%) reported at least 1 sensory symptom consistent with neuropathy (pain, paresthesias, and loss of sensation), and 335 (38.0%) reported neuropathic pain ranging from slight (116 participants [13.4%]) to severe (70 [7.9%]). Increasing numbers of abnormal HIV-SN examination findings were associated with increasing pain severity (P < .001). Among the 658 participants with no abnormal HIV-SN signs, 111 (16.9%) reported pain that had neuropathic characteristics as described above, except that its severity was typically slight (n = 58) or mild (n = 32).

### RISK FACTORS FOR NEUROPATHIC PAIN

**Table 2** presents unadjusted and adjusted ORs for selected risk factors for neuropathic pain compared with those with neuropathy without pain. Significant risk factors in univariate analyses were advancing age, previous exposure to D drugs, higher CD4 nadir, and greater CD4 recovery level. After adjusting for other factors, remaining risk factors were higher CD4 nadir and past D-drug exposure. Current D-drug use was associated with a lower risk of neuropathic pain.

#### RELATIONSHIP OF NEUROPATHIC PAIN TO DEPRESSION, EMPLOYMENT, AND DAILY FUNCTIONING

Of the participants, 74.0% were unemployed, 19.1% reported dependence in IADLs, and 14.6% met criteria for current major depressive disorder. After adjusting for CD4 current and nadirs, use of CART and D-drugs, plasma viral load, neuropsychological impairment, current major depression, and demographic factors such as age and education, the likelihood of being unemployed was significantly increased among participants with neuropathic pain of any severity (OR, 1.58 [95% CI, 1.18-2.11]). More severe pain was associated with a significantly greater likelihood of being unemployed. After adjusting for other significant predictors, the likelihood of being dependent in IADLs was significantly increased among participants with neuropathic pain compared with those without (OR, 2.29 [95% CI, 1.72-3.04]), and more severe pain was associated with more frequent dependence. Neuropathic pain was more frequent in participants with current major depressive disorder than in those without (OR, 1.95 [95% CI, 1.45-2.61]). Also, depressive symptoms were worse as measured by the Beck Depression Inventory II in those with neuropathic pain compared with those without (median [IQR], 17 [9-26] vs 9 [4-18]). However, among those with neuropathic pain, pain severity did not correlate with the severity of depressive symptoms (P = .45).
The median MOS-HIV physical health summary score was 45.5 (IQR, 35.6-55.6), which is worse than the average for participants in a pre-CART study that validated this measure for the assessment of quality of life. Individuals with more severe neuropathic pain scored lower on the MOS-HIV pain function subscale and quality of life subscales and the overall physical health summary. Participants with slight, mild, moderate, or severe pain together scored significantly lower compared with those with no pain on the MOS-HIV pain function subscale (median [IQR], 44.4 [33.3-66.7] vs 77.8 [55.6-100]; P < .001), quality of life subscale (50 [50-75] vs 75 [50-75]; P < .001), physical health summary (36.5 [30.1-44.5] vs 49.5 [40-57.5]; P < .001), and mental health summary (42.5 [35.2-50.7] vs 50 [40.9-56.8]; P < .001). The figure displays the relationship between MOS-HIV physical health summary scores and the presence and severity of neuropathic pain. Neuropathic pain explained 18% of the variance in MOS-HIV overall pain function, 3% of the variance in MOS-HIV mental health summary, and 13% of the variance in MOS-HIV physical health summary.

**COMMENT**

In a diverse cohort of more than 1500 men and women with HIV infection, we found that HIV-SN affected more than half. Despite improvements in the effectiveness and the tolerability of CART, HIV-SN prevalence was not lower than that seen in earlier studies. Neuropathic pain remained common and contributed to an excess burden of unemployment and disability.

The present study found the clinical correlates of HIV-SN to be somewhat different from those described before CART. Before CART, risk factors included advancing age, immunosuppression, ongoing D-drug use, and elevated plasma HIV viral load. Our study found that ongoing D-drug use and elevated viral load were no longer associated with increased risk. Furthermore, our analysis revealed new risk factors: current CART use and previous D-drug exposure. Age and worse immunosuppression remained strong predictors. The risk of HIV-SN was not related to CART effectiveness, indexed by undetectable plasma viral load. After adjusting for other factors, HIV-SN was not more frequent among the one-quarter of participants who were seropositive for HCV.

The elevated risk of HIV-SN in participants with low CD4 nadirs was independent of CART success as indexed by virologic suppression. Thus, among participants with virologic suppression, those who had started CART after their CD4 counts fell to less than 350 µL were significantly more likely to have HIV-SN than were those who started CART before the CD4 dropped to less than 350 µL, even after adjusting for age, estimated duration of HIV infection, and D-drug use. This finding suggests that it may be possible to protect patients from HIV-SN by initiating CART earlier than is recommended by current clinical guidelines. Participants in this study experienced substantial immune recovery on CART, averaging CD4 levels of more than 200 µL above their previous nadir. Because abnormal neuropathy signs persisted in about half despite virologic suppression and immune recovery, our findings imply that peripheral nerve recovery during CART is incomplete at best. One might speculate that CART itself is neurotoxic because it was associated with a higher HIV-SN prevalence even after adjusting for other factors, including D-drug exposure. Two previous studies suggested that HIV protease inhibitors might increase HIV-SN risk, but we previously performed a thorough assessment of this risk and found that the association was absent or markedly attenuated after considering other concomitant factors. However, CART use might be a surrogate for aspects of HIV disease severity not readily captured by available markers such as viral load and CD4 levels.

Although we did not work with a random sample, we believe that our results are likely to be generalizable to most patients receiving care for HIV in the United States. The sample size was large, and participants were recruited from multiple, geographically dispersed centers. Most participants were nonwhite, reflecting the demographics of the US epidemic, and, whereas previously published reports included predominantly individuals with more advanced disease, our study assessed many with early disease not yet requiring CART and numerous others who had experienced substantial recovery of CD4 levels with CART. Nevertheless, we cannot rule out the possibility of selection bias. The study was performed at centers with recognized ex-
pertise in the neurological complications of HIV. Although study enrollment was not contingent on participants’ reports of neurological symptoms or on physician referrals for neurological involvement, it is possible that those with cognitive impairment or neuropathy were oversampled. Furthermore, because study evaluations were lengthy and participants were paid a modest fee for their participation, those not employed may have been more likely to enroll.

Additional limitations of this study include its cross-sectional, observational design, which is by definition descriptive and precludes evaluation of causation. However, the prospective data collection, inclusion of multiple sites, and standardization of training and data collection tools across sites make this a robust characterization of the impact and clinical correlates of HIV-SN. Although we did not assess glucose control and other metabolic factors such as insulin resistance herein, these issues are being reported separately for a nested subgroup of participants who agreed to undergo measurement of fasting glucose and lipid levels.

Because pain is by far the most common reason to seek medical attention in HIV-SN, but not all patients experience pain, it would be quite useful to know what distinguishes those who become symptomatic from those who remain pain free. We found current but not past major depressive disorder to be a significant correlate of pain in HIV-SN, highlighting the potential role of mood state in the patient’s experience of neuropathic pain. We found that pain was more common among participants with relatively higher CD4 nadirs, suggesting that immune factors may play a role in susceptibility. Indeed, in a recent study, cytokine genotype influenced pain susceptibility after D-drug exposure, suggesting that inflammation contributes to pain pathogenesis.31 We also found that past, but not current, D-drug use was associated with an increased risk of pain in HIV-SN after adjusting for other factors. The relationship between D-drug use and painful HIV-SN has been previously reported.3 However, painful neuropathy does not affect all D-drug–treated individuals; many patients tolerate D-drug exposure for years without developing neuropathy signs or symptoms.32 If a patient using D drugs reports neuropathic pain, the prescribing physician usually switches to an alternative agent, which may explain why those with pain were less likely to be taking D drugs at the time of the study evaluation. Host genetic factors also may contribute to D-drug susceptibility. In 1 study, individuals with specific polymorphisms in the hemochromatosis (HFE) gene were more likely to experience painful neuropathy after D-drug exposure.33

CONCLUSIONS

With CART, HIV-infected individuals now live for decades. This study’s demonstration of the high prevalence of HIV-SN and its negative effect on patients’ quality of life underscores the need for novel treatment modalities to manage neuropathic pain and to promote neuroregeneration and recovery. Several novel pain management strategies are in development, such as cannabinoid receptor–modulating drugs, combination thera-
pies, and topical administration of high-dose capsaicin. A neuroprotective or neuroregenerative strategy would be attractive. However, no treatments to promote sensory nerve recovery have yet been shown to be effective and safe. Because individuals starting CART earlier in their HIV disease course have a lower risk of HIV-SN, it may be possible to prevent some cases of painful neuropathy through earlier treatment. Better understanding of the roles of inflammation and depression in painful neuropathy may lead to improved management.

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