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HIV Protease Inhibitors and Risk of Peripheral Neuropathy

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Abstract

Objective—Two recent analyses found that exposure to protease inhibitors (PIs) in the context of antiretroviral therapy (ART) increased the risk of distal sensory polyneuropathy (DSPN) in patients with HIV infection. These findings were supported by an in vitro model in which PI exposure produced neurite retraction and process loss in DRG sensory neurons. Confirmation of peripheral nerve toxicity with PIs could substantially limit their long-term use in HAART.

Methods—We evaluated current and past exposure to PIs as a risk factor for DSPN in 1159 HIV-infected individuals enrolled in a large, prospective, observational, multicenter study. Signs of DSPN were ascertained by neurological examination. Subjects were grouped into categories according to past and current exposure to any ARV and to PIs. We included disease indicators such as nadir CD4, plasma viral load, and duration of HIV infection, as well as advancing age and exposure to dideoxynucleoside ARVs in multivariate models.

Results—In univariate analyses, both past and current PI exposure significantly increased the risk of DSPN. However, after adjusting for previously validated concomitant risk factors in

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multivariate models, none of the PI exposure groups was more likely to have DSPN than ARV naïve subjects. A secondary evaluation of duration of PI use and exposure to individual PI drugs was similarly non-significant in multivariate models, except for small effects of amprenavir and lopinavir.

Interpretation—Evaluation of concomitant risks for HIV DSPN suggests that the independent risk attributable to PIs, if any, is small. This risk must be weighed against the important role of PIs in modern ART regimens.

BACKGROUND

Distal sensory polyneuropathy (DSPN), including both antiretroviral toxic neuropathy and primary HIV sensory neuropathy, is one of the most common neurologic complications of HIV infection ¹. DSPN causes pain and diminished exercise tolerance, resulting in reduced quality of life, disability and often requiring chronic analgesic medication use. Studies performed during the era prior to highly active antiretroviral therapy (HAART) showed that the risk and severity of DSPN were associated with advancing immunosuppression (lower CD4 cell count) and increased plasma HIV viral load ^{2, 3}. However, despite improvements in immune function and viral suppression with HAART, DSPN remains common ^{4–6}. Although certain components of HAART -- specifically, dideoxynucleoside ARVs (d-drugs) --- may account for persisting DSPN in some, the use of these drugs has declined, suggesting that d-drug neuropathy cannot fully explain the increasing numbers of individuals experiencing DSPN. Apart from the literature on the neurotoxicity of d-drugs and data suggesting that thermal thresholds improve in virological responders ^{7, 8}, data on the effects of HAART on DSPN are sparse. Recent studies have raised concerns about the potential neurotoxic impact of other HAART components (e.g., protease inhibitors), as well as metabolic disturbances such as insulin resistance and genetic susceptibility factors.

A recent study suggested that HIV protease inhibitors (PIs) may be among the components of modern HAART regimens that contribute to neuropathic pain and disability. Thus Pettersen et al ⁹ reported that the likelihood of DSPN was increased among patients with HIV infection exposed to PIs. Assessment of confounding conditions in these subjects was limited. Additionally, in DRG sensory neurons, exposure to the PI indinavir resulted in significant neurite retraction and process loss, suggesting neuronal toxicity.

The objective of this analysis was to further evaluate the relationship between PI exposure and DSPN while adjusting for potentially important confounders. If the link between PI exposure and DSPN is confirmed, this could provide a better understanding of the risks associated with PI use and prove to be a substantial limiting factor in the long-term use of protease inhibitors in HIV-infected individuals.

METHODS

The CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) study is a multicenter, prospective, observational study designed to determine the effects of HAART on the nervous system. The research was conducted at six North American locations: Johns Hopkins University, Baltimore, MD; Mt. Sinai School of Medicine, New York, NY; University of California, San Diego, CA; University of Texas, Galveston, TX; University of Washington, Seattle, WA; and Washington University, St. Louis, MO. Institutional Review Boards at each site approved all research and all participating subjects gave informed consent. The study's procedures include comprehensive neuromedical and laboratory assessments. Data from 1159 baseline evaluations for the presence or absence of DSPN between September 2003 and December 2006 were included in this cross-sectional analysis.

Distal Sensory Polyneuropathy (DSPN)

A complete neurological exam was performed by trained study clinicians (MDs and RNs) to determine whether signs of DSPN were present, including diminished ability to sense vibration on bilateral great toes, inability or decreased ability to discriminate between sharp and dull, and absent or weakened bilateral ankle reflexes. A diagnosis of DSPN was assigned if at least one of these signs in a symmetrical, bilateral pattern was present. Symptoms consistent with DSPN were collected by self-report including loss of sensation, hyperalgesia, tingling, pain, or burning in bilateral lower distal extremities.

ARV Usage

Duration of use, dosage and dosing frequency was obtained for all currently and previously used ARVs by clinician interview. This data was based on participant self-report; however, a sub-sample was verified by a review of medical records. This analysis focused on PI use; subjects were analyzed according to whether they had ever used specific PIs. PIs in use at the time of this analysis were amprenavir, nelfinavir, indinavir, atazanavir, lopinavir, saquinavir-HGC (SQV), saquinavir-SGC (SQV2), and tipranavir. Ritonavir was not analyzed separately because in most cases it was used as a booster for another PI. The lifetime duration of exposure to PIs was calculated in months based on reported start and stop dates.

Since the objective was to isolate the relationship of protease inhibitor use to DSPN while controlling for use of other ARVs, subjects were grouped into categories according to past and current exposure to any ARV and to PIs. Additionally, given the known neurotoxicity of dideoxynucleosides (d-drugs), data on current usage of stavudine, didanosine and zalcitabine, were used to classify subjects as d-drug-exposed or not.

Laboratory Measurements

Blood was collected by venipuncture. Plasma HIV viral loads were quantified by reverse transcriptase-polymerase chain reaction (Amplicor®, Roche Diagnostic Systems, Indianapolis, IN) using the ultrasensitive assay (nominal lower limit of quantitation, 50 c/mL). Viral loads were $\log_{10}$ -transformed prior to analysis to improve their distribution. Blood CD4 cell counts were measured by flow cytometry. CD4 nadir was determined by self-report. To determine the accuracy of this data, we compared the CD4 nadir reported at subjects' last visit to the lowest CD4 count measured during the course of study participation in a subset of subjects who were followed longitudinally and who began the study reporting a CD4 nadir at least as high as the measured CD4 count at their first study visit. Among this subgroup, reported CD4 nadir and actual CD4 nadir did not differ supporting the use of self-reported CD4 nadir for the present study.

Statistical Analysis

Univariate analyses were performed to assess demographic and clinical differences between subjects with and without DSPN and between ARV/PI groups using the Chi-square test for categorical variables and t-test or Wilcoxon rank sum for continuous variables, depending on whether the continuous variable was normally distributed. Unadjusted odds ratios of having DSPN were calculated using logistic regression with a single group status predictor. Adjusted odds ratios were calculated with age, exposure to d-drugs, CD4 nadir, plasma viral load and duration of HIV infection also included as predictors. All analyses were performed using JMP statistical package (version 6.0, SAS Institute Inc.).

RESULTS

Participant Characteristics

African-Americans and Caucasians represented 88% of the sample; 48% were African-American and 40% were Caucasian. Most of the sample was male (76%) with an average age of 43 years (standard deviation = 8 years). Approximately two-thirds of subjects were taking ARVs at the time of the study visit. The median CD4 count and plasma viral load were 418 (cells/mm³, Inter-quartile range [IQR] = 253–607) and 2.3 (log₁₀ c/mL, IQR = 1.7–4.1) and 63% were diagnosed with AIDS. 761 (66%) subjects had used PIs, 507 (44%) were on them at the time of their study evaluation.

DSPN was present in more than half of subjects (58%). Among those, symptoms were present in 58% (34% of the total number of subjects). A comparison of clinical and demographic characteristics between subjects with and without DSPN is presented in Table 1. Subjects with DSPN were about six years older on average (46 vs. 40 years, $p < 0.0001$), had a lower median CD4 nadir (121 vs. 223, $p < 0.0001$) and were more likely to have an AIDS diagnosis (72% vs. 51%, $p < 0.0001$). They were more likely to be on ARVs (80% vs. 60%, $p < 0.0001$) and thus had a lower median plasma viral load (1.9 vs. 2.8, $p < 0.0001$).

ARV and PI Exposure

As illustrated in Figure 1, subjects were grouped according to past and current exposure to any ARV and past or current exposure to PIs into the following categories: Group 1: ARV naïve ($n=164$), Group 2: past ARV use/no PIs ($n=64$), Group 3: past ARV and PI use ($n=107$), Group 4: currently on ARVs/never used PIs ($n=170$), Group 5: currently on ARVs/past PI use ($n=147$), Group 6: currently on ARVs and PIs ($n=507$). Selected characteristics that seemed likely to differ between these six groups were evaluated: age, CD4 nadir, plasma viral load and estimated duration of HIV infection. As expected, the groups did differ in these characteristics (Table 2). Subjects using ARVs at the time of the study visit (Groups 4–6) were older, had lower median CD4 nadir and lower median plasma viral loads than subjects not currently using ARVs (Groups 1–3). Current and past users of PIs (Groups 3, 5 and 6) had been infected with HIV longer than subjects who never used PIs (Groups 1, 2 and 4).

The odds of having DSPN were calculated for each group relative to the group of subjects who were ARV naïve (Group 1). All groups except Group 2 (past ARV users who never used PIs) were significantly more likely than ARV naïve subjects to have DSPN. Relative to ARV naïve subjects, the odds of having DSPN were highest among subjects who were currently on ARVs and had been exposed to PIs (Group 6 – current PI users: odds ratio [OR] = 4.0, 95% confidence interval [CI] = 2.8–5.9; Group 5 – past PI use: OR = 3.8, 95% CI = 2.4–6.1).

Concomitant risk factors (ORs presented in Table 3) were evaluated in multivariate models, including age, exposure to dideoxynucleoside reverse transcriptase inhibitors (d-drugs) and markers of HIV disease progression (CD4 nadir, plasma viral load, and duration of HIV infection). Random glucose was not included because it was unrelated to DSPN or exposure to ARVs and PIs. After adjusting for these risk factors, no group was more or less likely to have DSPN relative to ARV naïve subjects. The results were the same when the analysis was repeated after redefining DSPN as the presence of signs and symptoms. Among individuals exposed to PIs, those with DSPN had a significantly greater duration of exposure to PIs by about 16 months (37.9 vs. 21.9 months, $p < 0.0001$) however this association disappeared after accounting for the risk factors described above.

Exposure to Individual PIs

To identify whether specific PIs were associated with DSPN, the relationship between exposure to each PI and DSPN was evaluated. The numbers of subjects reporting past or current use of each individual PI were as follows: amprenavir n=66, saquinavir n=177, indinavir n=288, lopinavir n=335, nelfinavir n=338, atazanavir n=281, fosamprenavir n=41. In univariate analyses, exposure to each PI was associated with an increased odds of having DSPN relative to being PI naïve (Figure 2; amprenavir [OR=6.1, 95% CI=3.1–12.0], saquinavir [OR=3.6, 95% CI=2.4–5.3], indinavir [OR=3.4, 95% CI=2.5–4.7], lopinavir [OR=3.4, 95% CI=2.5–4.6], nelfinavir [OR=2.6, 95% CI=1.9–3.5], atazanavir [OR=2.4, 95% CI=1.7–3.2], fosamprenavir [OR=2.1, 95% CI=1.1–4.1]).

Separate multiple logistic regressions were performed to determine whether each PI was associated with DSPN relative to being PI naïve after adjusting for concomitant risk factors (age, d-drug exposure, CD4 nadir, plasma viral load and length of HIV infection). Only amprenavir (OR=2.7, 95% CI=1.2–6.4) and lopinavir (OR=1.7, 95% CI=1.1–2.7) were significantly associated with an increased likelihood of having DSPN. Exposure to other PIs was not associated with DSPN (saquinavir [OR=1.3, 95% CI=0.8–2.3], indinavir [OR=1.6, 95% CI=1.0–2.5], nelfinavir [OR=1.4, 95% CI=0.9–2.1], atazanavir [OR=1.4, 95% CI=0.9–2.1], fosamprenavir [OR=1.2, 95% CI=0.5–2.6]).

DISCUSSION

We found that in unadjusted, univariate analyses, exposure to antiretrovirals from the protease inhibitor (PI) class was associated with an increased frequency of HIV DSPN. However, this class effect was markedly attenuated and no longer statistically significant when adjusting for well-known concomitant risk factors. Generally, individuals exposed to PIs were older, had experienced more advanced HIV disease, and had greater exposure to neurotoxic d-drugs than those exposed only to ARV regimens that did not include PIs. These concomitant risk factors are each known to confer an elevated risk of neuropathy, and may account in part for the increase seen with PIs as a class.

In addition to evaluating PIs as a class, we also assessed individual drugs within the class. This approach might detect risk associations for individual agents that would be diluted in the combined class analysis. To do this, we compared the prevalence of DSPN in subjects who had been exposed to a given PI to its prevalence in subjects who had no PI exposure. Exposure to amprenavir and lopinavir, but not the other PIs, was significantly associated with DSPN in both univariate and multivariate analyses.

The identification of amprenavir and lopinavir as possible independent risk factors for DSPN is not consistent with prior findings. Thus Pettersen et al 9 reported that their subjects with DSPN had a higher proportion of exposure to ritonavir, saquinavir, and indinavir, rather than amprenavir or lopinavir. Our initial univariate analyses supported Pettersen's findings, but after adjusting for known risk factors, only amprenavir and lopinavir were linked to DSPN. Previous studies have shown that important risk factors for DSPN in HIV are more advanced immunosuppression^{2, 3} exposure to d-drugs^{10, 11}, and advancing age^{9, 12}. Since Pettersen et al. did not perform multivariate analyses, they could not correct for these concomitant risk factors.

Lichtenstein et al 4 reported an increased risk of DSPN with exposure to indinavir, ritonavir, nelfinavir, and saquinavir, rather than amprenavir and lopinavir. The discordance with our study's results may reflect longer duration of PI exposure for many of our subjects (median PI exposure 38 months) as compared to Lichtenstein et al (median indinavir exposure 5 months, for example). An additional possible explanation is differences in the specific

concomitant risk factors chosen for inclusion in multivariate analyses. Our multivariate analysis included age, current and nadir CD4, plasma viral load, d-drug exposure and duration of HIV infection, all of which have been shown previously to influence DSPN prevalence in HIV, whereas Lichtenstein et al. adjusted for these factors and also for diabetes mellitus, first measured viral load, and race, which are not robust risk factors for HIV DSPN. Since both our study (n=1159) and the Lichtenstein analysis (n= 2515) had substantial numbers of subjects, it is unlikely that statistical power explains the differences in results. The differences across studies in the specific PI agents that conferred increased risk and the relatively low odds ratios after multivariate adjustment suggest that the risk effects are not robust.

Another possible explanation for discordance in these studies' findings is the definitional criteria for DSPN. The Lichtenstein and Pettersen analyses included neuropathic pain and sensory symptoms as diagnostic criteria, whereas our study diagnosed DSPN based on the presence of at least one abnormal exam finding, regardless of whether neuropathy symptoms were present. By defining cases in this way we evaluated risk factors for less severe DSPN, but were less likely to exclude mild cases. To determine if this difference in definitional criteria accounted for the discrepancies in risk factor findings, we repeated our analysis, now including symptoms as part of the case definition. Neuropathic symptoms were present in 58% of our subjects with DSPN, making the prevalence of symptomatic neuropathy overall 33.6%. In these symptomatic subjects, PIs still were not associated with an independently elevated risk of DSPN.

Previous studies have demonstrated that the prevalence of DSPN depends on the number of abnormal exam findings required for diagnosis. Thus Ellis et al.¹³ applying a case definition that required 2 signs, found that 21% of 301 subjects had DSPN. Relaxing the definition to just one abnormal sign yielded a higher prevalence and greater sensitivity, but reduced specificity. In this study, we favored a less stringent definition, based on the rationale that HIV DSPN is a predominantly sensory neuropathy with prominent small fiber involvement, thus abnormal physical findings such as distal reflex reduction and distal vibratory loss, which depend primarily on the integrity of large sensory fibers, may be subtle. To assess whether a more stringent redefinition of DSPN might influence our findings, we redefined neuropathy to require two or more signs of neuropathy. In this secondary analysis, DSPN was present in 29.5% of the subjects. Univariate analysis demonstrated that exposure to each PI again was significantly associated with risk of DSPN relative to being PI naïve. However, after adjusting for concomitant risks as described above, lopinavir (OR=1.75 [1.11–2.77]), nelfinavir (OR=1.97 [1.25–3.13]), and saquinavir (OR=1.86 [1.09–3.21]) were associated with DSPN.

Some strengths and potential limitations of this analysis should be addressed. Although previous studies reported on fewer and older PIs, ours evaluated the broader spectrum of PIs (8) currently in use in modern clinical cohorts. Additional PIs such as darunavir and tipranavir continue to be introduced. Thus PI-based therapy likely will be part of the armamentarium available to clinicians for many years. Among the limitations of this study are that it was not a randomized trial, and it is possible that some unmeasured factor limited our ability to observe an increased risk with PIs. Furthermore, because participants in this study were seen at primarily at academic, tertiary care medical centers, prescribing conventions for PIs might differ from those used in community settings, possibly limiting the generalizability of our findings.

Nevertheless, in the absence of randomized trials evaluating PI use and DSPN, this large, multi-site, observational study with careful assessment of neuropathy symptoms and signs provides strong evidence that concomitant risk factors may contribute substantially to

associations between PIs and DSPN. The evidence linking specific PIs to DSPN is inconsistent, therefore further research is needed to conclusively identify which PIs, if any, may contribute to DSPN. The independent risk of DSPN attributable to PIs, is likely to be small and must be weighed against the important role of PIs in modern ART regimens.

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Figure 1.

Figure 2.

Table 1

Participant Characteristics (n=1159).

	DSPN: yes N=668	DSPN: no N=491	p value
Demographic Characteristics			
Caucasian ¹	251 (38%)	212 (43%)	0.05
Male ¹	514 (77%)	370 (75%)	0.53
Age, yrs ²	45.6 (7.9)	40.0 (8.1)	<0.0001
Clinical Characteristics			
AIDS ¹	480 (72%)	252 (51%)	<0.0001
CD4 Count ³	408.5 (237.7–589.5)	426 (279–633)	0.06
CD4 Nadir ³	121 (31–239.2)	223 (87–362)	<0.0001
Plasma Viral Load, (log ₁₀) c/mL ³	1.8 (1.6–3.4)	2.7 (1.6–4.2)	<0.0001
< 50 c/mL ¹	299 (45%)	174 (36%)	0.0013
HCV positive ¹	224 (34%)	105 (22%)	<0.0001
Length of infection, years ³	11.3 (6.4–15.23)	7.8 (2.2–13.0)	<0.0001
Glucose ³	93 (83–107)	92 (82–105)	0.31
ARV Characteristics			
On ARVs ¹	532 (80%)	292 (60%)	<0.0001
Duration of current regimen, months ^{3, 4}	11.6 (4.0–25.3)	8.82 (2.5–23.8)	0.07
Duration of exposure to PIs, months ^{3, 5}	37.9 (14.9–67.1)	21.9 (7.9–50.3)	<0.0001
D-Drug Usage ¹			<0.0001
Never Used	231 (35%)	283 (58%)	
Past Use	328 (49%)	132 (27%)	
Currently Using	109 (16%)	76 (15%)	
Total exposure to D-Drugs, months ³	12.2 (0–50.7)	0 (0–25.4)	<0.0001

DSPN=Distal-sensory polyneuropathy, HCV=Hepatitis C, ARVs=Antiretrovirals, PIs=Protease Inhibitors

¹No. (%)²Mean (Standard Deviation)³Median (Inter-Quartile Range)⁴Limited to subjects currently taking ARVs (n=824)⁵Limited to subjects exposed to PIs (n=761)

Table 2

(A) Median age, CD4 nadir, plasma viral load ($\log_{10}$ c/mL) and estimated duration of infection across groups. Individuals exposed to PIs (Groups 5 and 6) were older and had more advanced HIV disease (lower CD4 nadir) than those exposed only to ARV regimens that did not include PIs (Groups 2 and 4). (B) Univariate (unadjusted) odds of having DSPN relative to ARV naïve subjects (Group 1). (C) Odds of having DSPN relative to ARV naïve subjects after adjusting for age, exposure to d-drugs, CD4 nadir, plasma viral load and duration of HIV infection. (D) Odds of having DSPN (defined as presence of signs and symptoms) relative to ARV naïve subjects after adjusting for age, exposure to d-drugs, CD4 nadir, plasma viral load and duration of HIV infection.

Group	ARVs	PIs	(A)		Plasma VL	Years of HIV	(B)		(C)		(D)	
			Age, yrs	CD4 nadir			Unadjusted	Adjusted	Unadjusted	Adjusted	OR	95% CI
Group 1 *	Never	Never	40	380	4.27	2.1	1.0	1.0	1.0	1.0	1.0	
Group 2	Past	Never	40	282	4.33	9.7	1.4	0.8–2.5	0.6	0.2–1.5	0.5	0.1–1.7
Group 3	Past	Past	42	216	4.36	11.2	2.2	1.3–3.7	0.9	0.4–2.1	0.9	0.3–2.5
Group 4	Current	Never	44	187	1.69	6.3	2.8	1.8–4.4	1.4	0.7–2.7	1.6	0.6–3.9
Group 5	Current	Past	44	139	1.69	11.0	3.8	2.4–6.1	1.1	0.5–2.3	0.8	0.3–2.1
Group 6	Current	Current	44	86	1.69	11.5	4.0	2.8–5.9	1.6	0.9–2.7	1.5	0.7–2.9

VL= viral load, OR=odds ratio, CI=confidence interval

* Reference category

Table 3

Univariate Odds Ratios for Concomitant Risk Factors

Risk Factor	OR*	95% CI
Age (every 10 yrs)	2.40	2.04–2.83
CD4 nadir (every 100 cells)	0.75	0.70–0.81
d-drug exposure (Y/N)	2.57	2.04–3.22
Plasma Viral Load ($\log_{10}$)	0.81	0.74–0.89
HIV duration (every 5 yrs)	1.50	1.35–1.67

*
p value <0.001