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Journal

AIDS, 33(10)

ISSN

0269-9370

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Publication Date

2019-08-01

DOI

10.1097/qad.0000000000002240

Peer reviewed

HHS Public Access

Author manuscript

AIDS. Author manuscript; available in PMC 2020 July 24.

Published in final edited form as:

AIDS. 2019 August 01; 33(10): 1575–1582. doi:10.1097/QAD.0000000000002240.

Catechol-*O*-methyltransferase polymorphism Val^{158} Met is associated with distal neuropathic pain in HIV-associated sensory neuropathy

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Abstract

Background: Many of those aging with HIV suffer from distal neuropathic pain (DNP) due to HIV-associated sensory neuropathy (HIV-SN). Prior studies have linked chronic pain conditions to a variant of the catechol-O-methyltransferase (COMT), Val^{158}Met. This variant confers reduced enzymatic activity and results in higher synaptic dopamine levels. Here we examined the role of Val^{158}Met as a predictor of DNP in HIV-SN.

Methods: In 1044HIV-infected individuals enrolled in CNS HIV Antiretroviral Therapy Effects Research, an observational study across six US institutions, we characterized the relationship between Val^{158}Met and DNP in HIV-SN. Participants underwent neurologic examination and genotyping. Stratification into genetic ancestry groups was employed to eliminate bias due to genetic background.

Findings: Of 590 participants with HIV-SN, 38% endorsed DNP, 24% reported nonpainful symptoms of neuropathy (paresthesia and numbness), and 38% were asymptomatic. Compared with asymptomatic HIV-SN, Val^{158}Met was associated with 2.3 higher odds of DNP. There were no increased odds of nonpainful symptoms. The association remained significant after controlling for other risk factors for DNP: lifetime diagnosis of depression, older age, ancestry, cumulative exposure to dideoxynucleoside antiretrovirals, diabetes, and nadir CD4^{+}. Stratified by genetic ancestry, the association between Val^{158}Met and DNP was significant in European and African genetic ancestry.

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Author contributions: analyzed the data: J.X. and R.J.E. Wrote the article: J.X. and R.J.E. Assisted in statistical analysis: A.U. Participated in discussion of analysis results and commented on the article: J.X., R.J.E., A.U., S.L., D.F., W.S.B., J.H.A., J.K.

Conflicts of interest

There are no conflicts of interest.

Interpretation: Val^{158}Met may be a genetic marker for susceptibility to DNP in HIV-SN. Our findings support the notion that differences in pain processing mediated by COMT-related dopamine signaling play a role in susceptibility to DNP in HIV-SN. Because prior studies suggest that the COMT allele may influence dose-response relationships with opioid treatment, knowing COMT genotype could influence management.

Keywords

genetic risk factors; HIV; neuropathic pain

Introduction

The aging HIV-infected population has brought into new focus the importance of understanding chronic diseases associated with HIV. Despite the efficacy of combined antiretroviral therapies (cART) in viral suppression, immune recovery, and increased longevity, HIV-associated sensory neuropathy (HIV-SN) is common, especially in older people living with HIV [1]. Although some people with clinical findings of HIV-SN may never develop symptoms, a large proportion experience debilitating features of neuropathy such as numbness, paresthesias, and distal neuropathic pain (DNP). Among the many possible complications of HIV, DNP is particularly difficult to manage and is a cause of significant disability. DNP responds poorly to analgesic medications that are used to treat other types of neuropathic pain and has detrimental effects on mood, employment, functioning in daily activities, quality of life, and medication adherence [2–5].

Dopaminergic neurotransmission plays a central role in modulating pain perception and opioid analgesia [6]. Catechol-O-methyltransferase (COMT) is an important enzyme that metabolizes and inactivates catechol neurotransmitters dopamine, norepinephrine and epinephrine, and therefore, may act as a key modulator of neurotransmission [7,8]. Val^{158}Met is a common coding single-nucleotide polymorphism on the COMT gene on chromosome 22q11.2 that has been shown to have functional effects on enzymatic activity [6]. The Val^{158}Met variant of COMT results in a valine to methionine mutation at position 158, rs4680 and results in significantly reduced enzymatic activity [7,9]. This reduced breakdown of catecholamines causes increased levels of synaptic dopamine following its release, effectively increasing dopamine neurotransmission.

We hypothesized that the Val^{158}Met variant of the COMT gene modulates susceptibility to DNP among people living with HIV-SN. This study assessed the relationship between Val^{158}Met and neuropathic pain in a racially diverse, HIV-infected population, the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) cohort. CHARTER is the largest US-based prospective study of neurological complications in HIV/AIDS in the cART era [10].

With an established role in dopamine neurotransmission and relevance to a number of pain conditions, the COMT Val^{158}Met variant may be an identifiable genetic risk factor for neuropathic pain in HIV. Figure 1 illustrates the proposed relationship by which COMT predisposes HIV-infected individuals with HIV-SN to the development of DNP but not the nonpainful symptoms of paresthesias and numbness. Here we examine the role of Val^{158}Met as a predictor for DNP in HIV-SN.

Chronic pain affects about 116 million American adults –more than the total affected by heart disease, cancer, and diabetes combined, and that the total cost of medical care and lost productivity exceeds $600 billion [11]. DNP remains difficult to manage and responds poorly to conventional medications used for neuropathic pain, causing many to resort to second-line or third-line options such as opioid analgesics. This issue is particularly salient in the current landscape of opioid abuse and dependence, where a better understanding of DNP may help guide individualized medicine to avoid opioid-related toxicity. HIV peripheral neuropathy is an undertreated chronic pain condition that causes substantial disability and reduced quality of life among people living with HIV that must be addressed. An understanding of genetic risk factors and the biological mechanisms underlying DNP may help identify those at increased risk for DNP and inform better and more individualized therapeutic measures.

Methods

Study population

The CHARTER Study is a prospective, observational study conducted at six US locations: Johns Hopkins University, Baltimore, Maryland; Icahn School of Medicine at Mount Sinai, New York, New York; the University of California, San Diego, California; the University of Texas Medical Branch, Galveston, Texas; the University of Washington, Seattle, Washington; and Washington University, St Louis, Missouri. Institutional review boards at each site approved this research, and each participant gave informed consent. Data collection was standardized across centers and employed a protocol of comprehensive neuromedical, neurobehavioral, and laboratory assessments, including nadir $CD4^+$ T-cell count, cART history, D-drug exposure, history of a major depressive disorder (MDD), and demographic information (from structured interviews), as well as current $CD4^+$ T-cell count, HIV plasma viral load, and hepatitis C viral serology (from laboratory data).

A subset of CHARTER Study participants (N=1055) was selected for a cross-sectional genomic sub-study of peripheral neuropathy based on having minimal or moderate comorbid conditions that could confound the results of their neurocognitive assessment. Overall CHARTER study eligibility criteria included the ability to provide details of cART use and to undergo a structured interview and examination for signs and symptoms of HIV-SN. Individuals were excluded for active opportunistic infections, for serious psychiatric disorders such as schizophrenia, or for inability to cooperate with the clinical evaluation. Institutional review boards at each site approved this research, and each participant gave informed consent. Further details regarding CHARTER Study eligibility, enrollment, and assessment procedures have been reported previously [2].

Clinical evaluation

Physicians and nurses trained in neurological AIDS disorders performed standardized, targeted neurologic examination to assess the signs and symptoms of HIV-SN, including DNP, which were identified using criteria published previously [2,12]. HIV-SN was defined by the bilateral presence of at least one of the following signs at any visit: diminished ability to recognize vibration, reduced sharp-dull discrimination in the feet and toes, reduced ankle

reflexes. A more stringent requirement of two or more signs was used for confirmatory analyses. Controls did not have any of these signs or symptoms of peripheral nerve disease. Neuropathy symptoms assessed were bilateral numbness, paresthesias, and pain consistent with DNP (burning, aching, or shooting pain, subsequently referred to as DNP). In this study, a structured survey classified DNP into the following five severity levels, ranked from 0 to 4: none, slight (occasional, fleeting), mild (frequent), moderate (frequent, disabling), or severe (constant, daily, disabling, and requiring treatment with analgesics or other medications). A positive DNP finding was defined as pain with severity of greater than or equal to 1. A severe DNP finding used in sensitivity analysis was defined as pain severity greater than or equal to 2.

The clinical psychiatric assessment employed the WHO Composite International Diagnostic Interview, a standardized, lay-administered instrument, to capture past and current Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) diagnoses of MDD and substance use disorders (abuse and dependence) [13,14]. This assessment was important for ascertainment of exclusions and psychiatric covariates.

Current opioid use

Use of the following opioid drugs was documented in the CHARTER study and included in analysis: codeine phosphate, fentanyl transdermal, hydrocodone/acetaminophen, hydromorphone hydrochloride (HCL), methadone HCL, morphine drip, oxycodone, oxycodone HCL, propoxyphene HCL, acetaminophen w/codeine, hydrocodone/homatropine, levorphanol tartrate.

Genomic DNA isolation of Val^{158}Met

Genomic DNA was isolated from whole blood samples using PUREGENE (Gentra Systems Inc., Minneapolis, Minnesota, USA). Samples were subjected to whole-genome nuclear genotyping using the Affymetrix Genome-Wide Human SNP Array 6.0 platform (Affymetrix, Inc., Santa Clara, California, USA). The Val^{158}Met (rs4680) single-nucleotide polymorphism (SNP) of interest was present on the SNP array. Markers of ancestry were analyzed using EIGENSTRAT software to generate principal components [15]. Model-based clustering on the top three principal components, using the *mclust* R package (https://www.stat.washington.edu/mclust/), was used to assign individuals to genetic ancestry clusters [16].

Statistical analysis

The role of Val^{158}Met in susceptibility DNP in HIV-SN in the presence of confounders was evaluated by multivariable logistic regression. In our dominant model, the Val^{158}Met allele was analyzed as a dichotomous variable (variant present or absent). Odds of the Val^{158}Met compared with wild-type (WT) was evaluated for each subgroup of neuropathy symptoms, with the asymptomatic neuropathy group serving as the reference group within HIV-SN (Fig. 2).

Univariate analysis was performed to identify confounding factors. Age (continuous), sex (M/F), ancestry (African/European/admixed Hispanic), plasma viral load (continuous),

cerebrospinal fluid (CSF) viral load (continuous), $CD4^+$ nadir (continuous), lifetime MDD (Y/N), on ART (Y/N), hyperlipidemia (Y/N), diabetes (Y/N), cumulative D-drug exposure (continuous), viral suppression (Y/N), hepatitis C virus serologic status (Y/N), height (continuous), alcohol abuse or dependence (Y/N), and opioid abuse or dependence (Y/N) were considered as possible confounders. The variables found to have an association with DNP at a significance level of 0.05 in univariable analysis were then included in the multivariable logistic models.

Mixed (forward/backward), stepwise logistic regression was used with a *P* value stopping rule (probability to enter=0.25, probability to leave=0.1) to determine a final, reduced model that predicted DNP in HIV-SN. Variables associated with DNPat 0.05 significance level in the adjusted model are reported. All statistical analyses were performed using the JMP 13 statistical package (SAS Institute Inc, Cary, North Carolina, USA). Data are expressed as number (percentage), mean (SD), median (interquartile range), or odds ratio (OR) [95% confidence interval (CI)].

To evaluate the contributions of genetic background to the observed effect of Val^{158}Met across a genome-wide association study, participants were stratified into European, African, and admixed Hispanic ancestry groups using 10 principal components as a measure of genetic ancestry [16]. This strategy was employed to maximize power to detect true associations across genetically disparate populations by eliminating bias due to ancestry.

Results

Study cohort

Of the 1055 potential participants, 11 were missing data on genotype or neuropathy signs or symptoms and therefore excluded from analysis. Of the remaining 1044, most were non-European [612 (59%)], middle-aged [mean age, 43 (8.6) years] men. All participants were HIV positive and most [641 (61%)] met 1993 Centers for Disease Control and Prevention criteria for AIDS. The median nadir and current $CD4^+$ cell count levels were 175/μl (50–300/μl) and 428/μl (266–602/μl), respectively.

In Table 1, demographic and disease characteristics are compared between participants with DNP and those without. The minor allele frequency of Val^{158}Met (rs4680) in this sample was 0.40, similar to that published on gnomAD by the Broad Institute, minor allele frequency = 0.4608 (NCBI refSNP via ExAC).

Prevalence of Val^{158}Met in distal neuropathic pain, HIV-associated sensory neuropathy, and neuropathy

590 (57%) showed at least one sign of HIV-SN, and 290 (28%) showed at least two signs of HIV-SN. 300 (29%) of all participants endorsed DNP, with or without other neuropathy symptoms, and among those with HIV-SN, 227 (38%) had DNP. A small proportion of those with no signs of neuropathy on examination reported DNP as a symptom (73/454; 16%). 206 (20%) participants endorsed exclusively nonpainful neuropathy symptoms (paresthesias and loss of sensation) but not neuropathic pain. 86 (8%) endorsed only paresthesias, 42 (4%)

endorsed only loss of sensation, and 78 (7%) endorsed both paresthesias and loss of sensation.

Probability of the presence of the Val^{158}Met allele was significantly associated with increasing DNP severity by the Cochran–Armitage trend test (P<0.0001). To evaluate a possible gene dose effect, we compared the odds of having two copies (Var/Var) versus one copy (WT/Var) of Val^{158}Met for the outcome of DNP as compared with those with no symptoms [OR 1.1 (95% CI 0.6–1.8)]. The gene dose (one versus two copies of Val^{158}Met) was not associated with a significant difference in DNP severity rating (Pearson's chi-squared P value=0.99). Therefore, the Val^{158}Met variant was analyzed as a dichotomous variable (present or absent) in all subsequent analyses.

Among those with HIV-SN, having the Val^{158}Met allele was associated with a significantly higher odds [OR 2.3 (95% CI 1.6–3.4)] of DNP compared with asymptomatic HIV-SN (Fig. 3). In contrast, the Val^{158}Met variant was not significantly associated with nonpainful symptoms [paresthesias alone (OR 1.3 (95% CI 0.7–2.4)), numbness alone (OR 2.0 (95% CI 0.8–4.6)), or both (OR 1.6 (95% CI 0.9–3.0))]. Val^{158}Met increased the odds of DNP alone, compared with no DNP. Those with at least one Val^{158}Met allele had a higher odds of having more severe DNP as compared with those with less severe pain [OR 1.81 (95% CI 1.2–2.7)].

In univariate analyses DNP was significantly associated with the following confounding factors: older age, genetic ancestry, and lifetime history of MDD. The following were NS: female sex, higher CD4$^+$ nadir, being on current ART, hepatitis C virus serologic status, height, lifetime histories of alcohol abuse or dependence or opioid abuse or dependence, diabetes, longer cumulative D-drug exposure, and viral suppression (≤50 plasma).

Table 2 shows the adjusted odds ratios of a multivariable logistic regression model controlling for significant covariates and known predictors of DNP. To control for factors with an established role in DNP, the logistic regression model included cumulative D-drug use, diabetes, and nadir CD4$^+$ in addition to each of the predictors significantly associated with DNP in univariate analyses (Table 2). The Val^{158}Met variant remained significantly associated with DNP [adjusted OR=1.9 (95% CI 1.3, 2.9)].

To assess the clinical relevance of our findings, we analyzed the relationship between current opioid use and DNP. Of those with HIV-SN, 132 (22%) had current opioid use. Having DNP was associated with a significantly higher odds of current opioid use compared with asymptomatic HIV-SN [OR 2.0 (95% CI 1.2–3.2)].

Ancestry

Systematic allele frequency differences among ethnic groups and admixture can result in reduced power or false-positives in genome-wide association studies. To better understand how genetic background might contribute to the observed role of Val^{158}Met in DNP, participants were stratified into three groups by genetic ancestry: European, African, and admixed Hispanic [16]. TheallelefrequencyofVal^{158}Metwas0.52intheEuropean ancestry, 0.29 in African ancestry, and 0.43 in admixed Hispanic ancestry (P value <0.0001). The

Val^{158}Met allele was significantly associated with a higher odds of DNP than asymptomatic HIV-SN in those of European ancestry[OR 2.7 (95% CI 1.4–5.3, *P* value=0.004)] and of African ancestry [OR 1.8 (95% CI 1.0–3.0, *P* value=0.03)], but not the admixed Hispanic group [OR 1.5 (95% CI 0.4–5.7, *P* value=0.55)].

Discussion

We found that the presence of the COMT Val^{158}Met variant allele modified the clinical expression of HIV-SN, making DNP significantly more frequent. Our findings identify Val^{158}Met as a susceptibility factor for DNP in HIV, supporting the notion that differences in pain processing mediated by COMT-related dopamine signaling may play a role in the development of DNP in those with HIV-SN. The association of the Val^{158}Met allele was specific to DNP and not to nonpainful neuropathic symptoms, as predicted in the model in Fig. 1. We confirmed our hypothesis that the Val^{158}Met variant of the COMT gene modulates susceptibility to DNP among HIV-infected individuals.

A small proportion (15%) of participants reported DNP, but did not show signs of neuropathy on examination. This is not surprising as we have previously shown that even in the absence of clinical examination findings of HIV-SN, more sensitive studies (nerve conduction and quantitative sensory testing) reveal clear evidence of HIVSN (positive predictive value 96%) [12].

The relationship between opioid use and DNP underscores the clinical relevance of this study. Those with DNP had twice the odds of current opioid use compared with those without neuropathy symptoms. Opioid analgesics are generally considered second-line treatments for neuropathic pain but are often prescribed because DNP responds poorly to standard treatment strategies [17]. The most recent Cochrane review described the efficacy of opioids for chronic neuropathic pain as uncertain at best [18]. Since prior studies suggest that the COMT allele may influence dose–response relationships with opioid treatment, knowing COMT genotype could influence management. In the current climate of opioid abuse and dependence, it is especially important to understand the mechanisms of DNP and to keep addiction potential and long-term safety in mind when choosing treatment.

Zubieta *et al.* described a relationship between COMT Val^{158}Met and the experience of pain. Individuals homozygous for the Val^{158}Met reported higher sensory and affective pain ratings than wild-type controls, and this effect was demonstrated to be mediated by diminished activation of the μ-opioid receptor system [19]. Prior COMT studies have found associations between Val^{158}Met and low back pain, fibromyalgia, and morphine use for cancer pain, among other conditions. The Val^{158}Met allele is associated with long-lasting low back pain, sciatica, and disability after lumbar disc herniation [20]. Fibromyalgia patients homozygous for Met demonstrated higher sensitivity to thermal and pressure pain stimuli than patients with other genotypes [21]. Patients with cancer pain and the Val^{158}Met allele required less morphine than their wild-type Val counterparts [22,23]. The mechanism of the effect of COMT on human pain is not clear, but it does have potential in identifying patients at risk for developing pain in certain contexts and predicting clinical outcomes.

The COMT-mediated mechanisms underlying pain are likely differently across different causes of pain. Several association studies have failed to find an association of COMT polymorphisms to pain sensitivity. In a large, population-based Norwegian study, genotype and allele frequencies of the Val^{158}Met polymorphism were equally distributed between controls and individuals with musculoskeletal complaints, and the same cohort also showed no association between the Val^{158}Met polymorphism and migraine [24,25]. Most interestingly, a study of Spanish patients with neuropathic pain showed no association between genotypes of the Val^{158}Met polymorphism and susceptibility to neuropathic pain [26]. These contradictory findings further complicate our understanding of the role of COMT, particularly across different types of populations and pain modalities. Differences in study design and methodologies, such as the use of different pain measurement instruments, makes it especially challenging to interpret such findings. Our positive findings, in contrast with the negative findings in these two studies, suggest different biological pain mechanisms for HIV-related DNP versus musculoskeletal pain and neuropathic pain unrelated to HIV.

Using principal components to stratify the population by genetic ancestry, participants were sorted into one of three groups: European, African, or admixed Hispanic. This approach merits caution around potential inaccuracies in genomic ancestry group assignment, likely due to genetic admixture. However, only 20 participants (five among those with HIV-SN) self-reported an ethnicity other than black, white, or Hispanic, so we speculate that the relative contribution of mis-assigned participants to findings is minor [16]. Previous studies have similarly shown that the frequency of the COMT polymorphism varies substantially across different racial and geographical populations [27–29]. Although we found increased risk for DNP with Val^{158}Met across all three ancestry groups, the study was not powered to look at ancestry groups individually, especially in the case of the admixed Hispanic group. Nevertheless, the finding that Val^{158}Met had differential effects on DNP across the three genetic ancestry groups supports the notion that genetic background has an important modulatory effect on the relationship between COMT and DNP.

A number of comorbid conditions, such as diabetes mellitus and exposure to neurotoxins including dideoxynucleoside antiretrovirals (D-drugs), contribute to peripheral neuropathy in people living with HIV [30]. The clinical findings in these conditions do not reliably distinguish them from neuropathy due to HIV itself. History of MDD contributes to onset of DNP in HIV-SN [31]. We adjusted statistically to account these confounding factors. The Val^{158}Met polymorphism remained a valuable ‘genomic signpost’ for susceptibility to DNP in HIV infection.

Our study has both strengths and limitations. A strength is the rigor with which HIV-SN and DNP were defined [10,32]. Among the unmeasured variables, one limitation is potential differences between the cohort and the current population affected by HIV in the United States. Because CHARTER was designed to be a representative subset of people with HIV in the United States at the time of the original study (2003–2007), this cohort may be less representative of people with HIV infected from 2007 onward.

Within the COMT gene, Val^{158}Met is the best studied polymorphism, but other SNPs, particularly those in linkage disequilibrium, may contribute to DNP risk. Val^{158}Met (rs4680)

has been found to be in strong linkage disequilibrium with COMT polymorphism rs4633, which was demonstrated to have a similar pain modulatory effect to rs4680 in a study of treatment outcomes in low back pain [33]. A far less prevalent COMT polymorphism, rs6267, also encodes a substantially less active enzyme [34]. In the noncoding region of COMT, rs2075507 has been shown to alter mRNA expression with a minor effect on enzyme activity [7].

Other genetic polymorphisms may also contribute to differences in DNP, and the dopamine-mediated modulation of neuropathic pain by COMT is likely not an isolated effect. Dopamine-beta-hydroxylase (DBH), which catalyzes the conversion of dopamine to norepinephrine, is another enzyme involved specifically in catecholamine metabolism that has been found to have a possible interaction with COMT and merits future investigation in the context of neuropathic pain [35]. DBH polymorphisms were not represented on the SNP array we used. Additional genes governing upstream and downstream components of the dopamine signaling pathway other than degradation by COMT, such as synthesis, trafficking, packaging, and receptor function were not examined in this study but may be key modulators to investigate in future studies.

Future studies building upon our understanding of genetic determinants of DNP in HIV may help guide our choice of therapy in a burgeoning era of personalized medicine. An understanding of genetic risk factors may help identify people living with HIV at increased risk for HIV-SN with DNP and inform targeted preventive measures such as diabetes management, alcohol counseling, or cART initiation. These approaches are particularly relevant in the landscape of opioid abuse, as DNP remains difficult to manage with more conventional medications used for neuropathic pain. Further research into the pathogenesis of DNP may also allow for the development of more effective treatments.

Acknowledgements

The CNS HIV Anti-Retroviral Therapy Effects Research was supported by awards N01 MH22005, HHSN271201000036C, and HHSN271201000030C from the National Institutes of Health.

The CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) group is affiliated with Johns Hopkins University; the Icahn School of Medicine at Mount Sinai; University of California, San Diego; University of Texas, Galveston; University of Washington, Seattle; Washington University, St. Louis; and is headquartered at the University of California, San Diego and includes: Director: Igor Grant, MD; Co-Directors: Scott L. Letendre, MD, R.J.E., MD, PhD, Thomas D. Marcotte, PhD; Center Manager: D.F., Jr.; Neuromedical Component: R.J.E., MD, PhD (PI), J. Allen McCutchan, MD; Laboratory and Virology Component: S.L., MD (Co-PI), Davey M. Smith, MD (Co-PI).; Neurobehavioral Component: Robert K. Heaton, PhD (PI), J.H.A., MD, Matthew Dawson; Imaging Component: Christine Fennema-Notestine, PhD (PI), Michael J Taylor, PhD, Rebecca Theilmann, PhD; Data Management Component: Anthony C. Gamst, PhD (PI), Clint Cushman; Statistics Component: Ian Abramson, PhD (PI), Florin Vaida, PhD; Johns Hopkins University Site: Ned Sacktor, MD (PI), Vincent Rogalski; Icahn School of Medicine at Mount Sinai Site: Susan Morgello, MD (Co-PI) and David Simpson, MD (Co-PI), Letty Mintz, N.P.; University of California, San Diego Site: J. Allen McCutchan, MD (PI); University of Washington, Seattle Site: Ann Collier, MD (Co-PI) and Christina Marra, MD (Co-PI), Sher Storey, PA-C.; University of Texas, Galveston Site: Benjamin Gelman, MD, PhD (PI), Eleanor Head, R.N., B.S.N.; and Washington University, St. Louis Site: David Clifford, MD (PI), Muhammad Al-Lozi, MD, Mengesha Teshome, MD.

The views expressed in this article are those of the authors and do not reflect the official policy or position of the United States Government.

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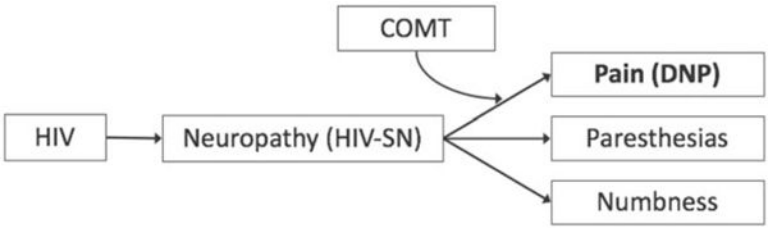

Fig. 1.
Proposed role of catechol-*O*-methyltransferase in neuropathic pain.

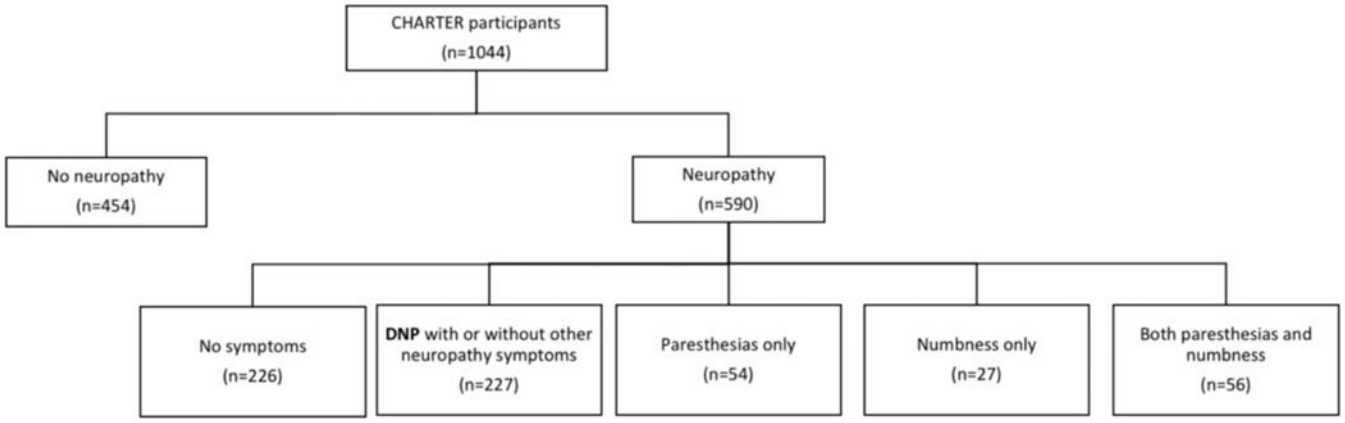

Fig. 2.
Categories of neuropathy symptoms.

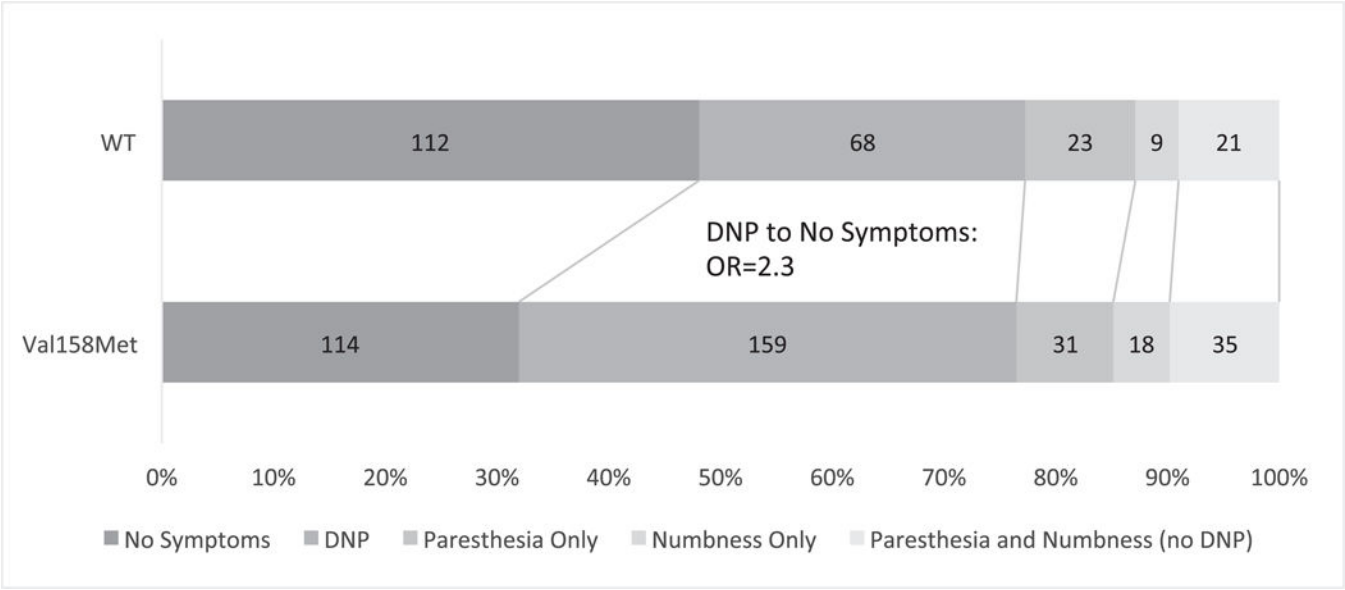

Fig. 3.

Relationship between Val^{158}Met and neuropathy symptoms in participants with HIV-associated sensory neuropathy. *N*=590.

Table 1.

CNS HIV Antiretroviral Therapy Effects Research genetic study population demographics.

Demographics	**Total**		**HIV-SN, *n*=590**		***P* value**
		Asymptomatic neuropathy	Neuropathy symptoms		
			DNP	Nonpainful symptoms only	
n	1044	226	227	137	–
Age, mean (SD)	43.1 (8.6)	44.4 (8.2)	46.2 (7.2)	46.4 (7.5)	0.013*
Male, *n* (%)	807 (77.3)	177 (30.0)	171 (29.0)	111 (18.8)	0.541
Ancestry, *n* (%)					0.001*
European	432 (41.4)	73 (12.4)	112 (19.0)	56 (9.5)	
African	484 (46.4)	133 (22.5)	98 (16.6)	68 (11.5)	
Admixed Hispanic	128 (12.3)	20 (3.4)	17 (2.9)	13 (2.2)	
Disease characteristics					
$CD4^+$ nadir, median [IQR]	175 [50, 300]	93 [30.8, 254]	135 [35, 247]	120 [16.5–233]	0.977
$CD4^+$ current, median [IQR]	428 [266, 601]	405 [233, 576]	461 [269, 600]	393 [251, 542]	0.062
Plasma VL (log_{10}), median [IQR]	2.28 [1.70, 4.0]	2.0 [1.7–3.9]	1.8 [1.7, 3.6]	1.8 [1.7, 3.2]	0.610
CSF VL (log_{10}), median [IQR]	1.70 [1.7, 2.4]	1.7 [1.7, 2.1]	1.7 [1.7, 2.1]	1.7 [1.7, 2.0]	0.619
On cART, *n* (%)	744 (71.3)	173 (29.3)	186 (31.5)	115 (19.5)	0.157
Cumulative D-drug exposure, median mos. [IQR]	0 [0, 27.6]	0.43 [0, 42]	6.8 [0, 43]	7.2 [0, 37.2]	0.614

Values in total column given as counts and percentages of all CNS HIV Antiretroviral Therapy Effects Research participants. Values in HIV-SN columns given as counts and percentages of those with HIV-SN. *P* values calculated for DNP (*n*=227) versus asymptomatic neuropathy sex (*n*=226). *P* values for ancestry, on cART, sex calculated by Pearson's chi-squared test. *P* values for continuous variables calculated by *t* test. cART, combined antiretroviral therapy; DNP, distal neuropathic pain; HIV-SN, HIV-associated sensory neuropathy; IQR, interquartile range; VL, viral load.

***P* value <0.05.

Table 2.

Adjusted multivariable analysis of distal neuropathic pain in CNS HIV Antiretroviral Therapy Effects Research participants with HIV-associated sensory neuropathy (n=435).

Predictor	Odds ratio (95% CI)	P value
Val^{158}Met variant	1.94 (1.29, 2.91)	0.001*
Lifetime MDD	1.81 (1.23, 2.67)	0.002*
Ancestry (ref: African)		
European	1.78 (1.15, 2.73)	0.009*
Admixed Hispanic	1.15 (0.55, 2.38)	0.716
Diabetes	2.08 (1.05, 4.12)	0.033*
Age	1.02 (1.00, 1.05) per year increase	0.094
Nadir $CD4^+$	1.00 (1.00, 1.00) per unit increase	0.546
Total D-drug exposure	1.00 (0.99, 1.00) per month increase	0.838

N=453 (226 HIV-SN with asymptomatic neuropathy and 227 HIVSN with DNP). CI, confidence interval; DNP, distal neuropathic pain; HIV-SN, HIV-associated sensory neuropathy; MDD, major depressive disorder.

*P value less than 0.05.