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Detrimental Effects of Psychotropic Medications Differ by Sex in Aging People with HIV

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Abstract

Background—Mental health (MH) conditions are common among persons with HIV (PWH). An understanding of factors associated with prescription medication use for these conditions and clinical impact of the prescription medications may improve care of MH disorders in PWH.

Methods—Psychotropic medication use was examined among PWH within the AIDS Clinical Trials Group A5322 (HAILO) study. Multivariable logistic models and Cox regression models estimated the association between psychotropic medications (any/none) with baseline and incident slow gait (>1 sec/m) and neurocognitive impairment (NCI) over 4 years.

Results—Of 1,035 participants, the median age was 51. 81% were men, 30% black, non-Hispanic, and 20% Hispanic. Psychotropic medication use was similar between men (34%) and women (38%; p=0.19). PWH using psychotropic medications had greater odds of baseline slow gait (OR 1.61, [95% CI 1.23–2.10]; p<0.001). Men but not women using psychotropic medications had an increased risk of developing slow gait (hazard ratio 1.85; [1.29–2.65] vs 0.77; [CI 0.35–1.68], p interaction=0.045). The sex-specific ORs for medication use and NCI were qualitatively but not statistically different (men: 1.79; [1.14–2.80]; women: 1.27; [0.56–2.90]; p interaction = 0.47). Psychotropic medication use was associated with an increased risk of incident NCI (HR 2.18; [95% CI 1.23–3.84], p=0.007) in both men and women.

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Conclusions—Psychotropic medications are associated with impairment in functional outcomes of aging, with a greater risk of baseline NCI and incident slow gait among men. Further investigation is needed to optimize outcomes in PWH and prescription of psychotropic medications among both men and women.

Keywords

Psychotropic Medications; adverse clinical outcomes

Background

In the United States, one in six people has a mental health disorder, costing nearly $200 billion in 2013.[1] Approximately 13% of adults are prescribed psychotropic medications,[2] with the use of antidepressants alone increasing almost twofold over the last 20 years.[3] Although medication is an essential component of comprehensive mental health care, many psychotropic medications have been associated with increased risk of geriatric syndromes including falls,[4,5] fractures,[6] slow gait speed,[7,8] and impairment in neurocognitive function.[9] Whether these outcomes are due to medications themselves, mental health disorders, or a combination is unclear. Furthermore, although some studies suggest a negative impact of psychotropic medications on gait speed[7,8] and neurocognitive impairment (NCI),[9] other studies suggest a protective effect, with improvements in functional outcomes with greater time on pharmacotherapy.[10]

Mental health disorders are more prevalent in persons with HIV (PWH)[11] than the general population, with some estimates suggesting a three-fold greater risk compared to people without HIV.[12,13] In PWH, depression has been linked with less virologic suppression and greater risk of AIDS-related illness and death,[14–16] particularly among persons not engaged in mental health care. Evidence suggests that mental health disorders in PWH are often underdiagnosed and undertreated.[17,18] Among PWH engaged in mental health care, treatment may involve a high burden of psychotropic prescription medications, with associated costs and adverse side effects. Importantly, many psychotropic medications can interact with antiretroviral therapy, which may increase adverse effects, particularly with the burden of polypharmacy among older PWH.[19,20] Although psychotropic medication use has been associated with falls among PWH in cross-sectional studies, the association with other clinical outcomes such as slow gait speed or NCI among PWH is not well described.[21]

Among PWH, women have high rates of depression (>40% in some studies),[22–24] and are more likely than men with HIV to be prescribed psychotropic medications,[25] perhaps due to higher mental health treatment-seeking behaviors. Despite treatment, studies of younger women (mostly <40 years of age) living with HIV and depression have shown greater rates of HIV disease progression and increased mortality compared to women without depression.[22,23,26] The goals of this analysis were to identify differences in psychotropic medication use and determine the effect on fundamental geriatric outcomes in a cohort of older men and women with HIV. We hypothesized that older PWH who used psychotropic medications would have greater risk for developing slow gait speed or NCI. Furthermore, we speculated

that women would have a greater rate of psychotropic medication use and thus poorer clinical outcomes than men.

Methods

Study Population

The HIV Infection, Aging, and Immune Function Long-Term Observational Study (HAILO) study, or AIDS Clinical Trials Group (ACTG) Study A5322, is a prospective observational study of PWH who were ≥40 years of age at the time of enrollment, had received randomized assignment of initial antiretroviral therapy (ART) through an ACTG trial, and were followed in the ACTG A5001 (ALLRT) observational study after their trial participation ended. The HAILO Study enrolled in 2013–2014, and participants are evaluated every six months. This analysis included 1035 individuals with gait speed or neurocognitive function measured at the A5322 entry visit, and for the analyses of incident slow gait and neurocognitive impairment (NCI), those who also had ≥1 additional gait speed or neurocognitive measurement through week 144. 581 participants (495 men and 86 women) were included in the incident gait speed analysis (400 participants with slow gait speed at study entry were excluded). Similarly, 793 participants (650 men and 143 women) were included in the incident NCI analysis (166 participants with NCI at entry were excluded).

Psychotropic Medications—Psychotropic prescription medications were used as a proxy for mental health diagnoses, as only limited primary mental health diagnostic data were collected (ongoing diagnosis of major depression, or ≥ grade 3 major depression symptoms using Division of AIDS criteria[27]). Psychotropic medications were self-reported or abstracted from chart review as available. Medications were first classified into eight categories to explore sex differences by types of prescribed therapies: first generation antidepressants, second and third generation antidepressants, first generation antipsychotics, addiction treatment medications, benzodiazepines, buspirone (a non-benzodiazepine anxiolytic), mood stabilizers and anticonvulsants, and sleep medications. Because numbers within each class were small, our primary analysis measured the impact of any psychotropic medication (vs none) on outcomes. In exploratory analyses, we further grouped medications into three overarching classes depending on psychotropic properties: sedating medications (e.g., benzodiazepines and sleep aids), stimulating medications (e.g., selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors) or neutral medications (e.g., buspirone and mood stabilizers/anticonvulsants). Opioid medication use was analyzed separately due to the known effects of opioid medications on neurocognition.

Outcomes—Gait speed was measured yearly as the average of 2 timed readings on a 4-meter walk, and times were dichotomized as ≤1 meters/second or >1 meters/second, as gait speed ≤1 meters/second in aging persons has been associated with poor prognosis, including increased hospitalizations and death.[28] Neurocognitive impairment (NCI) was assessed yearly using the ALLRT Neuroscreen[29], with sex, age, race/ethnicity and education-adjusted scores for Trails-Making A, Trails-Making B, and Digit Symbol. NCI was defined as having

≥1 test score ≥2 standard deviations below the mean, or ≥2 separate test scores that were ≥ 1 standard deviation below the mean.

Other Covariates—Insurance was categorized as: no insurance/unknown, public insurance (including Medicaid), Medicare, and private insurance. Education level was grouped as: less than high school completion, high school or GED completion, or greater than high school education (reported at first neurocognitive evaluation during ALLRT follow-up). Self-reported race/ethnicity was categorized as: white non-Hispanic, black non-Hispanic, and Hispanic. Smoking was defined as current, prior, or never smoker. Substance use status was self-reported as use of a non-prescribed psychoactive substance (marijuana, cocaine, heroin, amphetamines, or other non-prescribed drugs) at least once within the last month. Self-reported alcohol use was categorized as abstaining (no drinking); light (men: <7 drinks/week and no binging; women:<3 drinks/week and no binging [binging defined as ≥5 drinks/2 hour period for men, ≥4 drinks for women]); moderate (men: 7–14 drinks/week and no binging; women: 3–7 drinks/week and no binging); and heavy (men: >14 drinks/week, or binging; women: >7 drinks/week, or binging). All covariates were measured at A5322 entry unless otherwise indicated. As efavirenz use has been linked with neurocognitive impairment,[30,31] baseline efavirenz use was considered in NCI models only.

Statistical Analysis

Demographic characteristics were compared by any use versus no use of psychotropic medications, using chi-square and Wilcoxon tests for categorical variables and continuous variables, respectively. We fit separate logistic regression models to evaluate the associations between each socioeconomic variable (race/ethnicity, education and medical insurance) and any psychotropic medication use (overall and then stratified by sex). When the effect estimates for the sex-stratified models suggested qualitative sex differences (effect modification), we included an interaction term in the logistic regression models. Multivariable models were fit to adjust for age and/or race/ethnicity; additional covariates were entered into the model one at a time. If the covariate changed the odds ratio (OR) for medication use and the outcome by ≥10% it was retained in the final, multivariable model.

Logistic regression modeling was used to examine the association between medication use and prevalent outcomes of slow gait speed and NCI. Age was forced into all models and education was forced into the models for NCI. Multivariable models were fit to adjust for confounding and assessed for effect modification, as described above. Additional logistic regression models were fit to explore the association between medication class (stimulating, combination of sedating/stimulating, neutral) and prevalent slow gait speed and NCI.

Cox proportional hazards models were used to examine the association between psychotropic medication use and the outcomes of incident slow gait and NCI. These analyses were restricted to those without the outcome at entry and at least one additional visit through week 144. Participants without the outcome were censored on the date of their last evaluation. Date of outcome occurrence was defined as the midpoint from the previous evaluation to the date of the evaluation where the outcome was recorded. The same covariates described above were evaluated as potential confounding variables, and effect

modification was evaluated as described above. Since the assumption of proportional hazards was violated for several covariates in their original form, in the Cox proportional hazards models for incident NCI covariate categories were reduced for education (≤high school [HS] vs > HS), alcohol consumption (abstainer vs any alcohol consumption), and smoking status (non-smoker vs any smoking history).

Results

Of 1035 participants, the majority (81%) were men, white non-Hispanic (48%), privately insured (42%), with post-high school education (61%) and a median age of 51 years. Median CD4 count was 624 cells/μL, and 94% of participants were virally suppressed (HIV RNA <200 copies/mL) (Table 1). Marijuana was the most common substance used (17%), followed by non-prescribed medications (4%), and then cocaine (2%). At study entry, 705 participants (68%) were prescribed no psychotropic prescription medications, 193 (19%) were prescribed one, 75 participants (7%) were prescribed two, and 62 participants (6%) were prescribed three or more. The use of any psychotropic medication differed significantly by race/ethnicity, medical insurance, substance use, and smoking status, but not by sex (Table 1). The number of medications did not significantly differ between sexes. The most commonly-prescribed classes included second and third generation antidepressants (12% of participants), followed by mood stabilizers/anticonvulsants (11%). The type of medication class also did not differ by sex (i.e., 12% of men versus 13% of women were on second/third generation antidepressants, p=0.61; Table 2).

Demographic Characteristics Associated with Psychotropic Medication Use

In univariable analyses, Hispanic participants (OR=0.48 [95% confidence interval (CI) 0.33, 0.70], p<0.001) and Black non-Hispanic participants (OR=0.70 [0.52, 0.95], p = 0.02) had lower odds of psychotropic medication use compared to white, non-Hispanic participants. When stratified by sex, the odds for the association of Hispanic ethnicity with psychotropic medication use was substantially lower for women (OR=0.16 [0.06, 0.41]) than for men (OR=0.59 [0.39, 0.89], p interaction=0.013). This sex difference was not present for black (vs white) participants. Compared to those without insurance, the odds of taking psychotropic medications was greater for publicly-insured participants (OR=1.95 [1.31, 2.90], p=0.001) and participants on Medicare (OR=2.89 [1.80, 4.63], p<0.001) but similar to privately insured participants (OR=1.17 [0.81, 1.71], p=0.40). No associations were seen between education level and psychotropic medication use. The impact of insurance status and education level on psychotropic medication use did not vary by sex (Table 3).

In models adjusted for age, both Hispanic and Black individuals remained significantly less likely to take psychotropic medications, with sex differences remaining significant in the comparisons between Hispanic and white, non-Hispanic individuals. In models adjusted for age and race/ethnicity, the odds of taking psychotropic medications remained significantly greater for publicly-insured participants (OR=1.75 [1.16, 2.65], p= 0.008) and participants on Medicare (OR=2.43 [1.45, 4.08], p < 0.001) compared with those without insurance (Table 3).

Psychotropic Medication Use and Clinical Outcomes

At study entry, 419 (41%) participants had slow gait speed and 166 (17%) had NCI. Women were significantly more likely to have slower gait speed (54% vs 38%, p<0.001) and NCI (24% vs 15%, p=0.002) than men.

Gait speed—In models adjusted for age only, participants taking psychotropic medications had greater odds of baseline slow gait (OR=1.61 [1.23, 2.10], p<0.001) and greater odds of developing slow gait speed over time (HR=1.52 [1.10, 2.10], p=0.01) than those not on psychotropic medications. In sex-stratified models, the associations between psychotropic medication use and baseline gait speed were similar among men and women (OR=1.51 vs 2.09, respectively; p-value interaction=0.36). In the final multivariable models, psychotropic medication use remained significantly associated with slower baseline gait speed in both sexes (OR=1.95 [1.45, 2.61], p<0.001, Figure 1).

The age-adjusted association between psychotropic medication use and incident slow gait speed varied significantly by sex. When compared to men not taking psychotropic medications, men who took at least one psychotropic medication had higher incidence of developing slow gait speed (HR=1.85 [1.29, 2.65], p=0.002) -- a finding not seen among women (HR=0.77 [0.35, 1.68], p=0.15; p-value interaction=0.045; Figure 2).

Neurocognitive impairment—In models combining men and women, psychotropic medication use was not associated with NCI at baseline (OR=1.31 [0.92, 1.87], p= 0.13). In sex-stratified models, however, the association between medication use and baseline NCI was stronger among men (OR=1.60 [1.07, 2.41] than women (OR=0.71 [0.34, 1.48]; p-value interaction=0.059). In multivariable models including an interaction term for sex, psychotropic medication use was associated with baseline NCI in men (OR=1.79 [1.14, 2.80], p=0.01), but not women (OR=1.27 [0.56, 2.90], p=0.57; Figure 1); however, this effect modification was no longer statistically significant (p-value interaction=0.47).

Psychotropic medication use was also associated with incident NCI (adjusted HR=2.18 [1.23, 3.84], p=0.007; Figure 2), with no significant differences by sex. Efavirenz use did not change the effect estimate by ≥10% and was not kept in the multivariable model.

Effects of Medication Class on Outcomes

In multivariable analysis including the same variables, we next explored the effect of sedating or stimulating psychotropic medications. Participants on stimulating (OR=1.95 [1.21, 3.14], p=0.006), neutral (OR=2.44 [1.42, 4.22], p=0.001), and a combination of stimulating and sedating medications (OR=3.20 [1.64, 6.21], p<0.001) all had higher odds of having slow gait speed at study entry compared with those not taking psychotropic medications. Higher odds of baseline NCI were seen in participants taking sedating medications (OR=1.96 [1.07, 3.59], p=0.03) and participants taking a combination of stimulating and sedating medications (OR=2.69 [1.27, 5.65], p=0.009).

Opioid Medication Use

Lastly, we explored the additional effect that opioids may have as mood altering medications. Women were more likely than men to be prescribed an opioid medication (13% vs 5%, p <0.001). When analyses were repeated including opioids as a psychotropic medication, the number of participants taking one or more psychotropic medications remained similar (330 without opioids and 356 with opioids). Black participants no longer had lower odds of being on psychotropic medications compared to white participants (OR=0.81, [0.60, 1.09] p=0.16). The addition of opioids resulted in similar effects on baseline gait speed or NCI, and incident slow gait or NCI. The addition of opioids to sedating medications also resulted in similar outcomes.

Discussion

We have explored demographic factors associated with psychotropic medication use and clinical impact on functional outcomes of adults with well-suppressed HIV. Overall, with the exception of opioids, the class and number of prescribed of psychotropic medications were similar by sex, which is surprising in the context of literature suggesting higher rates of major depressive disorder among women than men with HIV.[11] Some differences in psychotropic medication use by demographics were identified, including higher use of medications in Medicare and publicly-insured participants and lower use in racial and ethnic minorities. Both men and women taking ≥1 psychotropic medications were more likely to have slower baseline gait speed and to develop NCI over time; in contrast, only men taking one or more psychotropic medications were more likely to have NCI at baseline and to develop slow gait speed than those men not on psychotropic medications.

Several of our findings merit further discussion: our finding that psychotropic medication use was associated with baseline slow gait speed is similar to prior studies linking depression[32,33] and psychotropic medications[7,8] to slow gait speed. The sex differences supporting more pronounced impact of these medications on men with regards to baseline NCI and incident slow gait are intriguing; sedating medication use was similar between men and women, and our models controlled for substance use. One possibility is a neuroprotective effect of estrogen in cognition-altering mental health disorders, especially schizophrenia.[34] This effect may be the reason that women with schizophrenia generally have later onset and less severe disease, and evidence suggests that treating schizophrenic patients with estrogen can improve their psychotic symptoms.[35] The association between baseline NCI and psychotropic medication use among men may explain the decline in gait speed of these men over time as well; previous studies have shown that baseline neurocognitive status predicts decline in gait speed and other physical function tests.[36,37]

The increased rate of psychotropic medication use among Medicare and publicly insured participants may reflect the high burden of mental health disorders, more consistent prescription medication coverage, or increased use of psychotropic medications due to a lack of counseling services. Indeed, evidence suggests that psychiatrists are less likely to take patients with Medicare and Medicaid than physicians of other specialties[38]. By contrast, lower use of psychotropic medications among Hispanic and African-American participants, and among Hispanic women compared to men may be due to differences in treatment

preferences and rates of depressive disorders. Hispanic-Americans and African-Americans with depressive disorders may be less likely than their white counterparts to find psychotropic medications acceptable for treatment.[39] Atypical presentations of mental health disorders among Hispanic women (e.g., somatization of depressive symptoms) may underestimate mental health disorders in this population.[40,41] With increased rates of depressive disorders in the poor and in the elderly[42] and worse clinical outcomes among racial minorities[43] and impoverished PWH,[44] the access to mental healthcare, cultural sensitivity in diagnosis of mental health disorders, and stigma associated with mental health treatment should be considerations among HIV primary care providers.

Lastly, we found that the combination of sedating and stimulating medications was associated with slow gait and NCI, with similar but attenuated associations with sedating medications or stimulating medications alone. Several of these medications can be found in the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults.[45] In our aging population, these medications can put patients at risk for adverse medication reactions and decreased clearance of medications.[45] The stronger negative effect on clinical outcomes among the participants on a combination of medications is not surprising: with at least two prescribed psychotropic medications in addition to at least three ART medications, participants met the definition for polypharmacy,[46] which has been associated with physical impairments[47] and functional decline.[48] The risk of polypharmacy holds especially true among older PWH, who are more likely than younger PWH to be prescribed medications that can cause dangerous drug-drug interactions with ART.[49]

Several limitations of this analysis should be acknowledged: our study population was predominantly men and has been consistently participating in clinical trials and observational studies for several years, and thus may not be representative of the overall population of PWH. With a limited proportion of participants with negative clinical outcomes, we were limited in the number of covariates that could be included in our models. Symptoms of mood disorders were not routinely assessed; thus, we were unable to assess the adequacy of treatment. Regarding NCI, medications used to treat the neurocognitive disorders other than stimulants were not included. Also, the ALLRT Neuroscreen is brief and does not provide comprehensive neurological testing. Finally, the rates of psychotropic medication use do not necessarily reveal the prevalence of mental health disorders, as participants may have declined medical therapy, may have utilized non-pharmacologic therapy, or may have stopped therapy due to cost, side effects, or stigma.

In conclusion, we found that psychotropic medication use may confer worse outcomes in terms of gait speed and neurocognition, among middle- and older-aged PWH, and especially among men. What remains unclear is whether mental health disorders, unmeasured confounders associated with mental health disorders, or the psychotropic medications were associated with poorer outcomes. Further research is needed to determine the adequacy of mental health treatment on clinical outcomes, and whether these effects differ by sex and among PWH.

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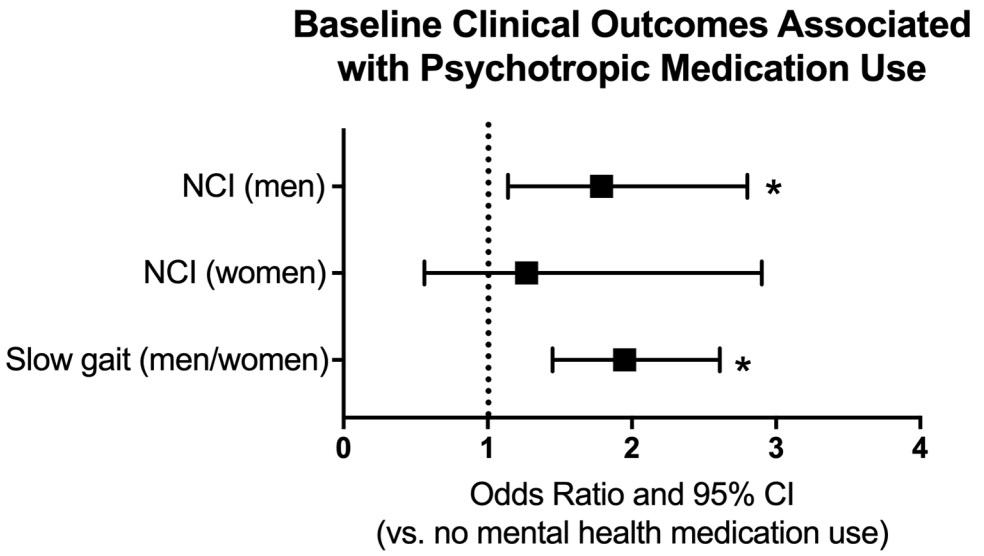

Figure 1:

Odds of baseline neurocognitive impairment (NCI), stratified by sex, and odds of baseline slow gait (men and women combined) associated with psychotropic medication use. NCI models are adjusted for age, race/ethnicity, substance abuse and an interaction between sex and medication use; gait speed models are adjusted for age and race/ethnicity; *$p<0.05$; separation of outcomes by sex is included only if there was a sex interaction in the outcome.

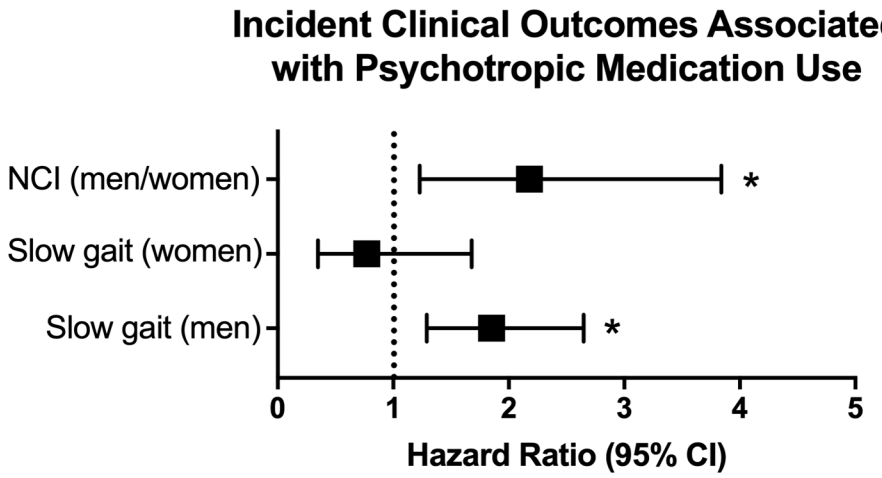

Figure 2:

Hazard of developing neurocognitive impairment (NCI; men and women combined), or slow gait (sex stratified) in association with psychotropic medication use. NCI models are adjusted for age, alcohol abuse, substance abuse, and smoking status; gait speed adjusted for age and interaction between sex and medication use; *p<0.05; separation of outcomes by sex is included only if there was a sex interaction in the outcome.

Table 1.

Demographic Characteristics at Study Entry by Psychotropic Medication Use

Medication Use at Study Entry					
Characteristic		**No psychotropic medication (N=705)**	**≥1 psychotropic medication (N=330)**	**Total (N=1035)**	**P-Value**
Sex	Male	570 (81%)	264 (80%)	834 (81%)	0.75
	Female	135 (19%)	66 (20%)	201 (19%)	
Age, years	Median (Q1-Q3)	50 (46–56)	51 (46–56)	51 (46–56)	0.39
Race/Ethnicity	White Non-Hispanic	307 (44%)	186 (56%)	493 (48%)	<.001
	Black Non-Hispanic	214 (30%)	91 (28%)	305 (29%)	
	Hispanic	160 (23%)	47 (14%)	207 (20%)	
	Other/Missing	24 (3%)	6 (2%)	30 (3%)	
Medical insurance	None/unknown	163 (23%)	52 (16%)	215 (21%)	<.001
	Public	164 (23%)	102 (31%)	266 (26%)	
	Private	315 (45%)	118 (36%)	433 (42%)	
	Medicare	63 (9%)	58 (18%)	121 (12%)	
Education	<High School	109 (15%)	44 (13%)	153 (15%)	0.50
	High School or GED	146 (21%)	78 (24%)	224 (22%)	
	>High school	428 (61%)	201 (61%)	629 (61%)	
Alcohol Consumption	Abstainer	277 (39%)	136 (41%)	413 (40%)	0.74
	Light Drinker	244 (35%)	104 (32%)	348 (34%)	
	Moderate Drinker	33 (5%)	18 (5%)	51 (5%)	
	Heavy Drinker	133 (19%)	66 (20%)	199 (19%)	
Substance use in past month	No	531 (75%)	236 (71%)	767 (74%)	0.008
	Yes	125 (18%)	85 (26%)	210 (20%)	
Smoking Status	Never	318 (45%)	108 (33%)	426 (41%)	<.001
	Prior Smoker	235 (33%)	112 (34%)	347 (34%)	
	Current Smoker	152 (22%)	110 (33%)	262 (25%)	
Absolute CD4 count (cells/μL)	Median (Q1-Q3)	624(455–833)	620(450–809)	624(451–828)	0.78
Virally Suppressed (<200 HIV-1 RNA copies/mL)	No	36 (5%)	21 (6%)	57 (6%)	0.41
	Yes	669 (95%)	209 (94%)	978 (94%)	

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Table 2.

Psychotropic Medication Prescription by Class

Percentage of Participants Prescribed Each Drug Class, by Sex			
Drug Class	**Men (%)**	**Women (%)**	**P value**
1st Generation Antidepressants	22 (3)	8 (4)	0.31
2nd and 3rd Generation Antidepressants	101 (12)	27 (13)	0.61
1st Generation Antipsychotics	40 (5)	12 (6)	0.49
Addiction Medications	3 (<1)	1 (<1)	0.78
Benzodiazepines	61 (7)	12 (6)	0.50
Buspirone	2 (<1)	0	0.49
Mood Stabilizers/Anticonvulsants	89 (11)	28 (14)	0.19
Sleep Medications	78 (9)	18 (9)	0.86
Opioids	44 (5)	26 (12)	<0.001

Table 3.

Associations between Demographic Information and Psychotropic Medication Use, Adjusted for Demographic Characteristics

Variables			Unadjusted Odds Ratio	Adjusted Odds Ratio (95% CI)	P value
Education (ref < high school)	High school /GED		1.16 (0.79, 1.72)	1.03 (0.64, 1.66) *	0.92
	>High school		1.32 (0.85, 2.07)	0.80 (0.51, 1.26) *	0.34
Race (ref White non-Hispanic)	Hispanic	Male	0.59 (0.39, 0.89)	0.59 (0.39, 0.90) +	0.01 (p-value for interaction)
		Female	0.16 (0.06, 0.41)	0.16 (0.06, 0.41) +	
	Black non-Hispanic	Male	0.69 (0.48, 0.99)	0.69 (0.48, 0.99) +	0.25 (p-value for interaction)
		Female	0.43 (0.21, 0.89)	0.43 (0.21, 0.89) +	
Insurance status (ref no insurance/ unknown)	Public (including Medicaid)		1.95 (1.32, 2.90)	1.75 (1.16, 2.65) *	0.008
	Medicare		2.89 (1.80, 4.63)	2.43 (1.45, 4.08) *	<0.001
	Private		1.17 (0.81, 1.71)	0.91 (0.60, 1.36) *	0.63

*Adjusted for sex, age, and race/ethnicity

+Adjusted for age

GED, general education diploma or high school equivalency certificate