

Substance Use Among HIV-Infected Patients Engaged in Primary Care in the United States: Findings From the Centers for AIDS Research Network of Integrated Clinical Systems Cohort

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More than 1 million people are currently living with HIV in the United States.¹ In multiple studies, including those involving probability samples, high rates of substance use have been observed among HIV-infected individuals.²⁻⁷ For example, in a nationally representative sample of 2864 HIV-infected adults, 40% reported having used an illicit drug other than marijuana in the preceding 12 months, and more than 12% had screened positive for drug dependence.⁸⁻¹⁰ In another study focusing on a multisite sample of 970 HIV-infected individuals recruited through outreach programs across 8 US cities, 40% of the respondents reported heavy alcohol use or crack-cocaine use in the preceding 12 months; 38% reported marijuana use, 14% reported heroin use, and 14% reported stimulant use over the same period.⁶ In addition, 25% had used 2 or more types of illicit drugs, excluding alcohol and marijuana.⁶

Substance use can have deleterious health consequences for people living with HIV.^{11,12} Prior research has shown that substance use affects HIV antiretroviral treatment, including self-care behaviors such as adherence to HIV medications, resulting in increased plasma HIV RNA and decreased CD4 cell counts.^{8,13-19} King et al. found that 62% of their sample of 193 HIV-infected individuals reported use of one or more drugs in the preceding 30 days, and this pattern of drug use was associated with significantly higher odds of having detectable (vs undetectable) plasma HIV RNA.¹⁶

In addition to affecting HIV medication adherence, substance use plays both a direct and an indirect role in HIV transmission.²⁰ Although many HIV-infected individuals eliminate or reduce behaviors that may increase the

Objectives. The purpose of this study was to better understand substance use behaviors and deleterious health consequences among individuals with HIV.

Methods. We examined a multicenter cohort of HIV-infected patients (n = 3413) receiving care in 4 US cities (Seattle, Birmingham, San Diego, Boston) between December 2005 and April 2010 in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS). We used generalized estimating equations to model specific substance use outcomes.

Results. Overall, 24% of patients reported recent use of marijuana; 9% reported amphetamine use, 9% reported crack-cocaine use, 2% reported opiate use, 3.8% reported injection drug use, and 10.3% reported polydrug use. In adjusted multivariable models, those who reported unprotected anal sex had higher odds of marijuana, amphetamine, injection drug, and polydrug use. An increased number of distinct vaginal sexual partners was associated with polydrug and crack-cocaine use. Nonadherence to antiretroviral therapy was associated with the use of all substances other than marijuana.

Conclusions. The co-occurrence of substance use, unprotected intercourse, and medication nonadherence could attenuate the public health benefits of test, treat, and link to care strategies. Prevention programs are needed that address these coprevalent conditions. (*Am J Public Health*. Published online ahead of print June 13, 2013; e1-e11. doi:10.2105/AJPH.2012.301162)

likelihood of HIV transmission (10% to 60% depending on the type of behavior, recall period, and partner serostatus), many others, particularly those who use illicit substances, do not necessarily consistently practice safe sexual behaviors.^{4,5,21-28} Parenteral drug use can transmit HIV directly through sharing of injection equipment and drug solutions,²⁰ and it can affect the spread of HIV indirectly through sexual behavior.^{29,30} Nonparenteral drug use has also been associated with higher odds of HIV transmission risk behavior, including unprotected vaginal and anal sex.^{27,31-33}

Substance use (including alcohol and nonparenteral drug use) influences people's cognitive capacity, impairs their decision making and judgment, and lowers their inhibitions, which can increase their probability of engaging in

high-risk sexual behaviors.²⁶⁻²⁸ The extent to which use of specific substances increases risky sexual behavior patterns among HIV-infected individuals, especially in the context of HIV disease characteristics (e.g., prescribed HIV medications, CD4 cell count, viral load), warrants additional study.

We sought to determine the patterns and prevalence of distinct substance use behaviors in a large, diverse multisite cohort of HIV-infected individuals receiving care in geographical locations throughout the United States. We examined the epidemiology of substance use alongside 4 health-relevant domains that can be used to guide future clinical interventions: sociodemographic characteristics, HIV disease characteristics (including medication adherence), comorbid psychological distress, and sexual risk behaviors.

We anticipated that, among HIV-infected patients, we would find disparities in substance use behaviors by age, gender, and race/ethnicity, with younger patients, members of racial/ethnic minority groups, and men exhibiting an increased risk of substance use. We also hypothesized that HIV medication nonadherence, psychological distress, and sexual risk behaviors would be associated with substance use behaviors. Finally, we predicted that there would be substantial variation in nonadherence, psychological distress, and risk behaviors according to the specific substance used.

METHODS

We examined HIV-infected patients receiving primary care services as part of the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) study. Initiated in January 1995, CNICS is an ongoing longitudinal observational investigation of HIV-infected patients enrolled in care at 8 clinical sites.³⁴

Participants

All HIV-infected patients aged 18 years or older who completed a CNICS clinical assessment of patient-reported outcomes as part of a routine clinical care visit before April 2010 were included in this study. The clinical assessment was integrated into clinical care between 2005 and 2008 at 4 participating sites: Fenway Health in Boston, Massachusetts; the University of Alabama at Birmingham 1917 HIV/AIDS Clinic; the University of Washington Harborview Medical Center HIV Clinic in Seattle; and the University of California, San Diego, HIV Clinic.

Patients complete the assessment every 4 to 6 months on average. In the case of patients who completed the assessment multiple times, only their first clinical assessment was included in our analyses. Data collection is ongoing. Patients who were medically unstable at the time of a visit, appeared intoxicated, had a cognitive impairment, or did not speak English or Spanish were not asked to complete the assessment.

Data Sources

The CNICS data repository captures longitudinal data on the CNICS cohort.³⁴ It integrates comprehensive clinical data from

outpatient and inpatient encounters, including standardized HIV-related information collected at enrollment (initial clinic visit) and clinical, medication, laboratory, and sociodemographic data obtained from each site's electronic medical record and other institutional data sources. Medication data are entered into patients' electronic medical records by clinicians; prescription fill–refill data are uploaded directly from pharmacy systems and verified through medical record reviews.

The CNICS data repository integrates patient-reported outcome data from the clinical assessment. Patients use touch-screen tablets or personal computers to complete the clinical assessment prior to their clinical encounter.

Analytic Approach

Primary outcomes. We used 6 indicators of nonparenteral and parenteral substance use as outcomes in our analyses. The Alcohol, Smoking and Substance Involvement Screening Test^{35,36} was used to collect data on substance use and to measure 6 binary outcome variables focused on recent (within the preceding 3 months) illicit substance use. Outcome variables were polydrug use (self-reported use of a combination of crack–cocaine, amphetamines, opiates, and marijuana), crack–cocaine use, amphetamine use, opiate use, marijuana use, and injection drug use.

Independent variables. We evaluated 4 groups of independent variables: sociodemographic characteristics; HIV disease characteristics, antiretroviral use, and HIV medication adherence behaviors; psychosocial factors; and sexual behaviors. The demographic factors assessed included age (continuous), gender, and race/ethnicity (White, Hispanic/Latino, Black, and other). We included geographical location (San Diego, Seattle, Birmingham, Boston) as a covariate in all of our statistical analyses to adjust for clustering.

HIV disease characteristics included viral load (detectable vs undetectable) and HIV medication use (currently or not currently taking HIV antiretroviral medications). Participants who reported taking HIV antiretroviral medications ($n = 2618$; 76.7%) were asked about medication adherence as part of their clinical assessment. A summary index to measure nonadherence was created from 4 items, as follows. First, the AACTG 4-day adherence

measure was to assess the number of HIV medication doses participants had missed in the preceding 4 days.^{37,38} Those who reported missing any doses were coded as nonadherent.

Second, participants were asked whether they had missed one or more doses of medication during the preceding weekend and were coded as nonadherent if they reported missing a dose. Third, participants were asked to indicate, via a self-rated item,³⁹ the last time they had missed a dose (never, more than 3 months ago, 1–3 months ago, 2–4 weeks ago, 1–2 weeks ago, within the past week). Participants who reported missing a dose sometime in the preceding 3 months were coded as nonadherent.

Finally, a 30-day visual analog scale (ranging from 0% to 100%) was used to assess how much of their HIV medication participants had taken in the preceding 30 days.^{38,40} Participants who reported having taken less than 90% of their medication in the past month were coded as nonadherent. A nonhierarchical (0–4) summary score was created from these 4 items.

The psychosocial factor domain included 3 categories: depression, symptoms of anxiety, and substance use treatment. We used the PHQ-9, a 9-item validated depression module of the Patient Health Questionnaire, to assess depression. The PHQ-9, which measures depressive symptomatology as well as functional impairment in the past 2 weeks, is based on the diagnostic criteria for major depressive disorder outlined in the *Diagnostic and Statistical Manual of Mental Disorders* (4th edition; *DSM-IV*).⁴¹ The instrument scores each of the 9 *DSM-IV* depression criteria on a scale ranging from 0 (not at all) to 3 (nearly every day), and thus standard PHQ-9 depression scores range from 0 to 27. The scale's Cronbach alpha coefficient in our sample was 0.91, consistent with previous research.⁴² Participants were categorized as having (score of ≥ 10) or not having (score < 10) clinical depression according to their continuous PHQ-9 scores and a previously validated cut point.⁴²

The PHQ-5, a 5-item validated anxiety module of the Patient Health Questionnaire, was used to assess symptoms of anxiety. The instrument's Cronbach alpha coefficient in our sample was 0.69. Participants were categorized as either having (score of ≥ 3) or not having (score below 3) clinical anxiety. Finally,

participants were asked whether or not they had accessed substance abuse treatment services in the preceding 12 months.

The final domain assessed was participants' sexual behaviors. Sexual behavior items focused on the number of sexual partners with whom participants had engaged in anal sex and vaginal sex during the preceding 6 months and whether or not they had engaged in unprotected anal and unprotected vaginal sex during this period.

Statistical analysis. We used generalized estimating equation (GEE) models in all of our analyses to adjust for the clustering by geographic location that resulted from the multisite CNICS design.^{43,44} The logit link function of PROC GENMOD was used in estimating regression models. For this procedure, we specified the variance–covariance structure as exchangeable (compound symmetry). SAS version 9.1.3 was used to analyze the data, and statistical significance was set at the .05 level.⁴⁵ A complete case analysis (listwise deletion) was used with the exception of scores for 2 variables. We used imputation procedures and means for completed scale items to singly impute missing depression scores ($n = 4$) and anxiety scores ($n = 26$).

We calculated descriptive statistics for each of the 6 substance use outcomes and variables that made up each of the 4 domains of independent variables. Bivariate GEE models were constructed to separately identify the variables within each domain that were significantly associated with each of the outcomes of interest. Within each domain, a blocked domain-specific model was fit that included only other variables within the same domain so as to optimize statistical power and minimize type 1 error.

We fit 4 separate multivariable models for each outcome. Across all models, age, gender, and race/ethnicity (White, Latino/Hispanic, Black, other) were included as statistical predictors.

Model 1 included all of the participants ($n = 3413$). In addition to sociodemographic characteristics, statistical predictors were current use of HIV medication, detectable viral load, depression, anxiety, and substance use treatment in the preceding year. Model 2 was restricted to participants who reported that they were currently taking HIV medication

($n = 2618$). Model variables included detectable viral load, depression, anxiety, substance use treatment, and medication nonadherence.

Model 3 was restricted to participants who reported having had anal sex in the preceding 6 months ($n = 1292$). Statistical predictors were current use of HIV medication, detectable viral load, depression, anxiety, substance use treatment, unprotected anal sex, and number of anal sex partners. Model 4 was restricted to participants who reported having had vaginal sex in the preceding 6 months ($n = 656$). Predictors were current use of HIV medication, detectable viral load, depression, anxiety, substance use treatment, unprotected vaginal sex, and number of vaginal sex partners. We did not fit Model 4 for injection drug use outcomes owing to insufficient sample sizes.

RESULTS

Our analyses focused on participants' sociodemographic characteristics in addition to multivariable model data.

Participant Characteristics

Table 1 presents the characteristics of the CNICS study sample. The majority of the participants were male (84%), and nearly half (46.2%) were members of racial/ethnic minority groups (11% Latino/Hispanic, 30% Black, 4.8% other). Participants were geographically diverse (30% from Seattle, 40% from Birmingham, 20% from San Diego, and 10% from Boston).

Nearly half (46.6%) of the patients had detectable plasma HIV RNA levels; among those taking antiretroviral medications, 34.0% had detectable HIV RNA levels. More than three fourths (76.7%) of the participants reported taking HIV medication at the time of the study. Only 30.6% of patients taking antiretroviral medications reported being fully adherent across the 4 indicators used to measure adherence behaviors.

More than 40% of the participants met the criteria for major depression, and 30% had clinical anxiety. Approximately 10% of the patients reported that they had accessed substance abuse treatment in the preceding 12 months. More than one third (37.9%) reported engaging in anal sex in the past 6 months with a mean number of 2.38 ($SD = 1.90$) sexual

partners. More than half (60.6%) of those reporting any anal sex reported unprotected anal sex during this time frame. Approximately 19% of the sample reported vaginal sex in the past 6 months with a mean number of 2.64 ($SD = 2.87$) sexual partners. Nearly half (46.04%) of those engaging in vaginal sex reported unprotected vaginal sex in the preceding 6 months.

There were geographical variations in substance use. Patients in Boston (odds ratio [OR] = 2.73; 95% confidence interval [CI] = 1.80, 4.14) and Seattle (OR = 3.02; 95% CI = 2.23, 4.08) had increased odds of crack–cocaine use relative to patients in Birmingham (the reference group in all of the models); patients in Boston (OR = 7.23; 95% CI = 4.28, 12.21), Seattle (OR = 8.05; 95% CI = 5.21, 12.44), and San Diego (OR = 10.58; 95% CI = 6.79, 16.50) had increased odds of amphetamine use; patients in San Diego (OR = 2.04; 95% CI = 1.01, 4.09) and Seattle (OR = 2.89; 95% CI = 1.59, 5.27) had increased odds of opiate use; and patients in Seattle (OR = 1.45; 95% CI = 1.19, 1.76), Boston (OR = 1.96; 95% CI = 1.49, 2.58), and San Diego (OR = 2.05; 95% CI = 1.66, 2.53) had increased odds of marijuana use.

In addition, patients in San Diego (OR = 8.31; 95% CI = 3.38, 20.42), Boston (OR = 11.48; 95% CI = 4.42, 29.83), and Seattle (OR = 12.11; 95% CI = 5.18, 28.30) had increased odds of injection drug use. Finally, patients in Boston (OR = 3.72; 95% CI = 2.44, 5.67), Seattle (OR = 4.05; 95% CI = 2.94, 5.58), and San Diego (OR = 4.36; 95% CI = 3.10, 6.13) had increased odds of polydrug use.

Multivariable Models

Overall, 10.3% of participants reported polydrug use in the preceding 3 months. In terms of self-reported substance use in the preceding 3 months, 24.3% of the participants reported marijuana use, 9.0% reported amphetamine use, 8.5% reported crack–cocaine use, 2.8% reported injection drug use, and 2.1% reported opiate use. Results of GEE models for each substance use outcome are presented in Table 2 (polydrug and marijuana use), Table 3 (amphetamine and crack–cocaine use), and Table 4 (opiate and injection drug use).

TABLE 1—Demographic and Clinical Characteristics of Patients in the Centers for AIDS Research Network of Integrated Clinical Systems Cohort: United States, 2005–2010

Characteristic	Sample, No. (%) or Mean \pm SD
Demographic characteristics	
Age, y	44.71 \pm 9.80
Geographic location	
San Diego, CA	685 (20.07)
Seattle, WA	1035 (30.33)
Birmingham, AL	1379 (40.40)
Boston, MA	314 (9.20)
Gender	
Female	545 (15.97)
Male	2868 (84.03)
Race/ethnicity	
White	1837 (53.82)
Hispanic/Latino	378 (11.08)
Black	1035 (30.33)
Other	163 (4.78)
HIV disease characteristics and medication adherence	
Currently taking HIV medications	2618 (76.71)
Detectable viral load	1590 (46.59)
Any HIV medication nonadherence in past 3 mo	1817 (69.40)
Nonadherence score (range = 0–4)	1.27 \pm 1.16
0	801 (30.60)
1	876 (33.46)
2	526 (20.09)
3	264 (10.08)
4	151 (5.77)
Psychosocial factors	
Depression	1395 (40.87)
Depressive symptoms	14.76 \pm 6.43
Anxiety	1010 (29.59)
Anxiety symptoms	3.21 \pm 2.01
Substance abuse treatment in past y	333 (9.76)
Substance use in past 3 mo	
Polydrug use	351 (10.28)
Marijuana use	828 (24.26)
Amphetamine use	308 (9.02)
Crack-cocaine use	290 (8.50)
Injection drug use	97 (2.84)
Opiate use	73 (2.14)
HIV sexual risk behavior	
Anal sex in past 6 mo (n = 1292)	
Unprotected anal sex	783 (60.6)
No. of anal sex partners	2.38 \pm 1.90
Vaginal sex in past 6 mo (n = 656)	
Unprotected vaginal sex	302 (46.04)
No. of vaginal sex partners	2.64 \pm 2.87

Note. Adherence variables were based on patients receiving antiretroviral therapy (n = 2618). The sample size was n = 3413.

Across all outcomes, younger age was associated with higher odds of using each substance (Tables 2–4). Gender-specific differences were also observed, with male patients having increased odds of polydrug, marijuana, amphetamine, and crack-cocaine use relative to female patients. Odds of opiate use, by contrast, were lower among men than women. After adjustment for potential confounders, there were racial differences in polydrug, marijuana, amphetamine, crack-cocaine, and injection drug use. Relative to White participants, Latino/Hispanic and Black participants had decreased odds of marijuana, amphetamine, and injection drug use but increased odds of crack-cocaine use.

In multivariable models that included the summary index measure of medication nonadherence, nonadherence in the preceding 3 months was associated with all substance use outcomes ($P < .05$) other than marijuana use. Detectable viral load was associated with polydrug, crack-cocaine, and injection drug use. Depression, anxiety, and drug treatment were significantly associated with substance use as well (Tables 2–4). Major depression was associated with a 1.5-fold to 3.0-fold increase in the odds of substance use in the preceding 3 months, with odds varying according to the specific substance used. Engaging in anal sex was associated with polydrug, marijuana, amphetamine, opiate, and injection drug use, whereas risk behaviors related to vaginal sex were associated with polydrug and crack-cocaine use.

DISCUSSION

The findings of this diverse multisite US study of HIV-infected individuals enrolled in primary care suggest that sociodemographic characteristics, HIV disease characteristics, adherence to antiretroviral medications, comorbid psychosocial health factors, and sexual risk are all associated with substance use and that these factors vary according to the substance used. Our results support regular screening for nonparenteral and parenteral drug use in primary care settings where HIV-infected patients are treated. Specifically, they support US Public Health Service guidelines that focus on the need for comprehensive HIV-related care that incorporates screening for substance use

TABLE 2—Bivariate, Blocked, and Multivariable Model Results for Polydrug Use and Marijuana Use in the Past 3 Months: Centers for AIDS Research Network of Integrated Clinical Systems Cohort: United States, 2005–2010

Characteristic	Bivariate Models, ^a Crude OR (95% CI)	Blocked Models, ^b Adjusted OR (95% CI)	Model 1 ^c (n = 3413), Adjusted OR (95% CI)	Model 2 ^d (n = 2618), Adjusted OR (95% CI)	Model 3 ^e (n = 1292), Adjusted OR (95% CI)	Model 4 ^f (n = 656), Adjusted OR (95% CI)
Polydrug use						
Demographic characteristics						
Age, y	0.97** (0.96, 0.98)	0.97** (0.96, 0.98)	0.98** (0.97, 0.99)	0.98** (0.97, 0.99)	0.99** (0.98, 0.99)	0.99 (0.98, 1.01)
Gender	1.71** (1.26, 2.31)	1.73** (1.20, 2.51)	2.01** (1.55, 2.61)	2.06** (1.52, 2.79)	0.98 (0.38, 2.52)	1.87** (1.5, 2.12)
Latino/Hispanic (vs White)	1.03 (0.93, 1.13)	0.94 (0.84, 1.05)	1.10 (0.98, 1.23)	0.92 (0.66, 1.27)	1.27* (1.01, 1.60)	0.80 (0.48, 1.36)
Black (vs White)	1.18 (0.95, 1.46)	1.20 (0.89, 1.61)	1.21 (0.94, 1.56)	1.05 (0.76, 1.44)	1.17 (0.88, 1.56)	1.31* (1.04, 1.66)
Other (vs White)	0.93 (0.59, 1.48)	0.90 (0.55, 1.49)	1.00 (0.61, 1.61)	1.25 (0.80, 1.94)	1.24 (0.50, 3.04)	1.40 (0.87, 2.28)
HIV disease characteristics and medication adherence						
Currently taking HIV medications	0.57** (0.45, 0.73)	...	0.82 (0.58, 1.15)	...	0.99 (0.56, 1.74)	0.89 (0.50, 1.59)
Detectable viral load	1.89** (1.61, 2.21)	1.34* (1.06, 1.68)	1.45** (1.22, 1.72)	1.21* (1.01, 1.46)	1.33 (0.92, 1.92)	1.55** (1.31, 1.82)
Nonadherence score	1.52** (1.26, 1.83)	1.48** (1.23, 1.79)	...	1.39** (1.16, 1.66)
Psychosocial factors						
Major depression	2.23** (2.01, 2.47)	1.73** (1.58, 1.88)	1.79** (1.64, 1.96)	1.48** (1.29, 1.71)	1.93** (1.77, 2.09)	1.39** (1.24, 1.57)
Anxiety disorder	2.02** (1.42, 2.88)	1.40 (0.90, 2.18)	1.38 (0.92, 2.07)	1.21 (0.84, 1.74)	1.76** (1.30, 2.39)	1.35 (0.90, 2.02)
Drug treatment	4.06** (3.81, 4.33)	3.39** (3.09, 3.72)	3.33** (3.08, 3.61)	3.40** (3.14, 3.69)	2.40** (1.87, 3.0)	2.94** (2.19, 3.95)
HIV sexual risk behavior						
Unprotected anal sex	2.27** (1.92, 2.67)	1.83** (1.49, 2.24)	1.54** (1.28, 1.86)	...
No. of anal sex partners	1.32** (1.22, 1.42)	1.27** (1.19, 1.35)	1.23** (1.15, 1.31)	...
Unprotected vaginal sex	1.21 (0.79, 1.87)	1.20 (0.78, 1.83)	1.05 (0.76, 1.45)
No. of vaginal sex partners	0.93** (0.90, 0.97)	1.18** (1.13, 1.23)	1.07** (1.04, 1.09)
Marijuana use						
Demographic characteristics						
Age, y	0.98** (0.97, 0.99)	0.98** (0.96, 0.99)	0.98** (0.87, 0.99)	0.98* (0.97, 0.99)	0.99 (0.97, 1.01)	0.96** (0.95, 0.97)
Gender	1.97** (1.41, 2.75)	1.86** (1.40, 2.46)	1.97** (1.41, 2.74)	2.31** (1.38, 3.86)	1.55 (0.82, 2.93)	1.94** (1.47, 2.56)
Latino/Hispanic (vs White)	0.84* (0.70, 0.99)	0.77** (0.63, 0.93)	0.81** (0.69, 0.95)	0.73** (0.56, 0.96)	0.90 (0.62, 1.30)	0.90 (0.45, 1.81)
Black (vs White)	0.77** (0.69, 0.86)	0.81** (0.70, 0.93)	0.83* (0.73, 0.95)	0.75** (0.61, 0.92)	0.97 (0.74, 1.27)	1.24 (0.86, 1.79)
Other (vs White)	0.95 (0.74, 1.20)	0.92 (0.71, 1.19)	0.96 (0.77, 1.21)	1.17 (0.85, 1.61)	0.88 (0.53, 1.46)	1.77 (0.90, 3.49)
HIV disease characteristics and medication adherence						
Currently taking HIV medications	0.85* (0.75, 0.97)	...	0.95 (0.84, 1.09)	...	1.01 (0.92, 1.12)	0.83 (0.49, 1.40)
Detectable viral load	1.21** (1.15, 1.28)	1.04 (0.94, 1.15)	1.08 (0.98, 1.20)	0.99 (0.89, 1.10)	1.02 (0.83, 1.26)	1.38* (1.06, 1.78)
Nonadherence score	1.13 (0.99, 1.29)	1.13 (0.99, 1.28)	...	1.10 (0.98, 1.24)
Psychosocial factors						
Major depression	1.62** (1.21, 2.18)	1.49** (1.31, 1.70)	1.51** (1.30, 1.75)	1.41** (1.33, 1.50)	1.56** (1.25, 1.94)	1.31 (0.86, 2.00)
Anxiety disorder	1.46 (0.86, 2.38)	1.22 (0.75, 1.99)	1.19 (0.73, 1.93)	1.17 (0.70, 1.96)	1.65** (1.30, 2.10)	1.90* (1.02, 3.55)
Drug treatment	1.32** (1.16, 1.50)	1.19* (1.04, 1.36)	1.15* (1.01, 1.32)	1.05 (0.91, 1.23)	0.74** (0.64, 0.85)	1.36 (0.87, 2.13)

Continued

TABLE 2—Continued

HIV sexual risk behavior									
Unprotected anal sex	1.26** (1.10, 1.45)	1.20** (1.07, 1.34)	1.13* (1.00, 1.28)
No. of anal sex partners	1.12** (1.08, 1.17)	1.08** (1.04, 1.12)	1.06** (1.02, 1.11)
Unprotected vaginal sex	1.03 (0.76, 1.40)	1.02 (0.72, 1.44)	0.93 (0.71, 1.21)
No. of vaginal sex partners	0.78** (0.69, 0.89)	1.21 (0.97, 1.51)	1.12 (0.92, 1.35)

Note. CI = confidence interval; OR = odds ratio. Generalized estimating equations were used to fit logit models to adjust for geographic location (the design covariate in all models was study site).
^aResults from fitted bivariate logistic regression models.
^bResults from multivariable logistic regression models examining block group baseline factors (e.g., domain-specific variables) associated with substance use.
^cIncludes all participants. Statistical predictors were age, gender, race/ethnicity, currently taking HIV medication, detectable viral load, depression, anxiety, and substance use treatment in the preceding year.
^dRestricted to participants who reported currently taking HIV medications. This model included the same variables as model 1 with the addition of medication nonadherence.
^eRestricted to participants who reported anal sex in the preceding 6 months. This model included the same variables as model 1 with the addition of unprotected anal sex and number of anal sex partners.
^fRestricted to participants who reported vaginal sex in the preceding 6 months. This model included the same variables as model 1 with the addition of unprotected vaginal sex and number of vaginal sex partners. The model was not fit for the injection drug use outcome owing to an insufficient sample size.
 P* < .05; *P* < .001.

and mental health as well as referrals to tertiary services. Our findings also provide evidence of the continued need to offer providers specific recommendations when working with HIV-infected individuals who use substances.

Population-level disparities in substance use by age, gender, and race/ethnicity have been documented in the United States.⁴⁶ We found sociodemographic disparities among HIV-infected patients in care. Consistent with our hypotheses, after other factors had been taken into account, substance use in the preceding past 3 months, with the exception of crack–cocaine use, was more common among younger patients. Male patients were more likely than female patients to report polydrug, marijuana, amphetamine, and crack–cocaine use, whereas female patients were more likely to use opiates.

In addition, race-specific disparities in crack–cocaine use were observed, with Black participants more likely to use crack–cocaine than White participants. Latino/Hispanic and Black participants had decreased odds of marijuana, amphetamine, and injection drug use relative to White participants. These findings with respect to sociodemographic disparities document the social epidemiology of substance abuse among HIV-infected populations and have implications for clinical practice, including the delivery and refinement of substance use prevention and treatment services for specific subgroups of HIV-infected individuals in care.

Consistent with previous research documenting the potential deleterious health consequences of substance use among people living with HIV,^{8,13–18} and in support of our hypotheses regarding HIV disease characteristics and adherence to antiretroviral medications, we found that nonadherence to HIV medications was significantly associated with recent substance use. Specifically, a higher frequency of nonadherence behaviors in the preceding 3 months was significantly associated with polydrug, amphetamine, crack–cocaine, opiate, and injection drug use. In addition, detectable viral load was associated with polydrug, crack–cocaine, and injection drug use after adjustment for medication adherence.

This latter finding suggests an association between poorer HIV disease management and polydrug, crack–cocaine, and injection drug use independent of medication nonadherence.

Overall, our results provide evidence of the continued need to offer providers specific clinical care–related recommendations formulated by expert panels (including the federal government, academics, and clinicians treating patients) so that they can improve their delivery of care to HIV-infected people who use substances.

For example, current guidelines on the prevention and treatment of opportunistic infections in HIV-infected adults⁴⁷ and guidelines on sexually transmitted infection screening in HIV-infected populations as a whole⁴⁸ both incorporate specific recommendations for people with HIV who use illicit drugs. One of these recommendations is to enroll active users into drug or alcohol treatment programs. In addition, injection drug users who are unwilling or unable to discontinue their drug use should be advised not to share needles or drug preparation equipment so that they reduce their risk of transmission; they should also be provided current information about how to access needle exchange programs in their areas.

As was the case in previous research,^{8,49} we found that mental health problems were common in our HIV-infected population, with 40.9% of participants meeting the criteria for depression and 29.6% meeting the criteria for anxiety. In addition, psychosocial distress at clinical threshold levels was associated with substance use behaviors. Moreover, 10% of participants reported having accessed substance abuse treatment in the past 12 months, and recent treatment was significantly associated with substance use outcomes.

Additional training for substance use treatment facility personnel concerning HIV-related health behaviors, including risk reduction interventions and management of HIV infection with attention to disease stage, may be beneficial in providing care for individuals seeking treatment. Similarly, ensuring that they are aware of the availability of substance abuse treatment services and primary care protocols that include follow-up treatment may benefit clinical practice.

As found in previous studies of sexual risk behaviors among HIV-infected individuals,^{3,4,17–24} the majority of patients in our study engaging in sex reported not having used condoms one or more times during anal sex or

TABLE 3—Bivariate, Blocked, and Multivariable Model Results for Amphetamine Use and Crack-Cocaine Use in the Past 3 Months: Centers for AIDS Research Network of Integrated Clinical Systems Cohort: United States, 2005–2010

Characteristic	Bivariate Models, ^a Crude OR (95% CI)	Blocked Models, ^b Adjusted OR (95% CI)	Model 1 ^c (n = 3413), Adjusted OR (95% CI)	Model 2 ^d (n = 2618), Adjusted OR (95% CI)	Model 3 ^e (n = 1292), Adjusted OR (95% CI)	Model 4 ^f (n = 656), Adjusted OR (95% CI)
Amphetamine use						
Demographic characteristics						
Age, y	0.97** (0.96, 0.98)	0.96** (0.95, 0.97)	0.96** (0.95, 0.97)	0.96** (0.94, 0.98)	0.98** (0.97, 0.99)	0.97* (0.94, 0.99)
Gender	2.20* (1.17, 4.16)	2.19* (1.00, 4.79)	2.97* (1.22, 7.19)	2.45** (1.49, 4.03)	1.35 (0.77, 2.37)	1.30 (0.94, 1.82)
Latino/Hispanic (vs White)	0.86** (0.76, 0.96)	0.75** (0.66, 0.85)	0.85 (0.66, 1.10)	0.68 (0.45, 1.03)	1.05 (0.88, 1.25)	0.91 (0.44, 1.91)
Black (vs White)	0.66** (0.52, 0.83)	0.63** (0.44, 0.88)	0.60* (0.39, 0.92)	0.55** (0.36, 0.84)	0.48* (0.27, 0.85)	0.43* (0.19, 0.98)
Other (vs White)	0.92 (0.61, 1.41)	0.88 (0.53, 1.48)	1.00 (0.58, 1.72)	0.89 (0.58, 1.36)	1.45 (0.74, 2.84)	1.18 (0.67, 2.07)
HIV disease characteristics and medication adherence						
Currently taking HIV medications	0.65** (0.49, 0.85)	...	0.77 (0.45, 1.31)	...	0.76 (0.43, 1.33)	0.82 (0.44, 1.52)
Detectable viral load	1.51** (1.23, 1.85)	1.10 (0.79, 1.53)	1.13 (0.81, 1.58)	0.98 (0.71, 1.35)	0.87 (0.61, 1.25)	1.00 (0.53, 1.87)
Nonadherence score	1.46** (1.16, 1.82)	1.44** (1.15, 1.82)	...	1.41** (1.13, 1.77)
Psychosocial factors						
Major depression	2.34** (2.27, 2.41)	1.78** (1.76, 1.80)	2.04** (1.86, 2.24)	1.74** (1.40, 2.16)	1.87** (1.52, 2.30)	1.67** (1.13, 2.46)
Anxiety disorder	2.27** (2.03, 2.55)	1.64** (1.38, 1.95)	1.68** (1.51, 1.87)	1.30** (1.10, 1.55)	1.67** (1.45, 1.93)	2.38* (1.16, 4.85)
Drug treatment	2.92** (2.46, 3.45)	2.42** (1.83, 3.19)	0.95 (0.68, 1.23)	2.51** (1.97, 3.19)	2.55** (2.12, 3.08)	2.05* (1.03, 4.05)
HIV sexual risk behavior						
Unprotected anal sex	3.77** (2.53, 5.63)	2.87** (1.90, 4.34)	2.39** (1.61, 3.57)	...
No. of anal sex partners	1.38** (1.28, 1.49)	1.37** (1.25, 1.50)	1.33** (1.21, 1.47)	...
Unprotected vaginal sex	1.13 (0.74, 1.74)	1.18 (0.74, 1.88)	1.04 (0.62, 1.76)
No. of vaginal sex partners	1.03 (0.97, 1.08)	0.91 (0.73, 1.13)	0.81 (0.63, 1.04)
Crack-cocaine use						
Demographic characteristics						
Age, y	0.99 (0.97, 1.00)	0.99 (0.98, 1.00)	1.00 (0.99, 1.01)	0.99 (0.98, 1.00)	1.00 (0.99, 1.01)	1.03** (1.02, 1.03)
Gender	1.01 (0.83, 1.23)	1.16* (1.01, 1.33)	1.22** (1.08, 1.38)	1.33 (0.90, 1.97)	1.09 (0.50, 2.38)	1.20* (1.00, 1.44)
Latino/Hispanic (vs White)	1.25** (1.10, 1.42)	1.20** (1.07, 1.35)	1.33** (1.21, 1.46)	1.26 (0.92, 1.72)	1.62* (1.11, 2.35)	0.96 (0.65, 1.43)
Black (vs White)	1.97** (1.57, 2.47)	1.98** (1.53, 2.55)	1.90** (1.57, 2.30)	1.94** (1.58, 2.39)	2.49** (1.61, 3.86)	1.71** (1.29, 2.28)
Other (vs White)	1.12 (0.76, 1.66)	1.11 (0.74, 1.66)	1.16 (0.85, 1.57)	1.44* (1.03, 2.01)	1.12 (0.38, 3.27)	1.36 (0.77, 2.38)
HIV disease characteristics and medication adherence						
Currently taking HIV medications	0.51** (0.39, 0.66)	...	0.80 (0.59, 1.09)	...	1.05 (0.56, 1.98)	0.71 (0.40, 1.27)
Detectable viral load	2.29** (1.70, 3.09)	1.61* (1.05, 2.47)	1.69** (1.25, 2.30)	1.48* (1.00, 2.20)	1.36 (0.68, 2.71)	1.71** (1.28, 2.28)
Nonadherence score	1.58** (1.40, 1.80)	1.52** (1.34, 1.73)	...	1.36** (1.21, 1.54)
Psychosocial factors						
Major depression	2.11** (1.71, 2.59)	1.37* (1.00, 1.89)	1.57** (1.26, 1.97)	1.60** (1.21, 2.12)	1.96** (1.24, 3.11)	1.60 (0.94, 2.73)
Anxiety disorder	1.94** (1.69, 2.22)	1.66** (1.27, 2.17)	1.34** (1.07, 1.67)	1.44** (1.22, 1.69)	1.79** (1.31, 2.45)	0.95 (0.54, 1.67)
Drug treatment	3.49** (2.17, 5.60)	2.97** (1.90, 4.64)	2.58** (1.83, 3.65)	2.80** (2.08, 3.77)	1.34 (0.65, 2.77)	2.10* (1.18, 3.73)

Continued

TABLE 3—Continued

HIV sexual risk behavior									
Unprotected anal sex	1.54* (1.09, 2.18)	1.45* (1.05, 2.00)	1.33 (0.95, 1.86)
No. of anal sex partners	1.13 (0.99, 1.30)	1.11 (0.98, 1.26)	1.08 (0.95, 1.22)
Unprotected vaginal sex	1.53** (1.18, 1.99)	1.46** (1.14, 1.87)	1.23 (0.94, 1.62)	...
No. of vaginal sex partners	1.02 (0.98, 1.06)	1.34** (1.19, 1.50)	1.26** (1.11, 1.42)	...

Note. CI = confidence interval; OR = odds ratio. Generalized estimating equations were used to fit logit models to adjust for geographic location (the design covariate in all models was study site).

^aResults from fitted bivariate logistic regression models.

^bResults from multivariable logistic regression models examining block group baseline factors (e.g., domain-specific variables) associated with substance use.

^cIncludes all participants. Statistical predictors were age, gender, race/ethnicity, currently taking HIV medication, detectable viral load, depression, anxiety, and substance use treatment in the preceding year.

^dRestricted to participants who reported currently taking HIV medications. This model included the same variables as model 1 with the addition of medication nonadherence.

^eRestricted to participants who reported anal sex in the preceding 6 months. This model included the same variables as model 1 with the addition of unprotected anal sex and number of anal sex partners.

^fRestricted to participants who reported vaginal sex in the preceding 6 months. This model included the same variables as model 1 with the addition of unprotected vaginal sex and number of vaginal sex partners. The model was not fit for the injection drug use outcome owing to an insufficient sample size.

* $P < .05$; ** $P < .001$.

vaginal sex in the past 6 months. Also consistent with previous research,⁷ we found that sexual risk behaviors were associated with substance use behaviors and varied according to the substance used. Anal sex risk behaviors were associated with polydrug, marijuana, amphetamine, opiate, and injection drug use, whereas vaginal sexual risk behaviors were associated with polydrug and crack-cocaine use.

These findings suggest the need for ongoing HIV prevention and risk reduction programming in primary care settings to address substance use behaviors.^{50,51} Also of note, sexual risk behavior indicators, including unprotected anal sex and number of anal partners in the past 6 months, were associated with amphetamine use in the past 3 months, replicating the associations documented in previous studies.⁵²⁻⁵⁶

Engaging in unprotected anal sex and having a greater number of anal sexual partners in the past 6 months were associated with marijuana use in the past 3 months. Mixed findings have been reported in the adult research literature on the association between sexual risk indicators and marijuana use; however, event-level analyses with younger populations have shown that marijuana use before sex significantly decreases the likelihood of condom use, with stronger sex-related marijuana expectancies moderating the association.⁵⁷ Given other research showing the high prevalence of marijuana use among HIV-infected individuals, and given that the effects of marijuana use on cognitive functioning differ by HIV disease stage, additional research is needed to understand sexual risk behaviors associated with marijuana use.⁵⁸

Finally, HIV sexual risk behavior, including unprotected anal sex and number of anal sexual partners in the past 6 months, was strongly associated with injection drug use in the past 3 months. This finding corroborates previous research^{59,60} and suggests the need for HIV risk reduction interventions specifically targeting injection drug users and men who have sex with men who also inject drugs. Additional research that considers sexual risk and substance use patterns in the context of HIV disease stage is necessary.⁶¹

Limitations and Strengths

A few limitations warrant consideration in interpreting our findings. Namely, because this

was a cross-sectional study, we were unable to consider temporality in modeling our exposures and substance use outcomes. For example, although we found that depression was associated with substance use, we were unable to empirically investigate the possibility of reverse causation, that is, whether psychological distress was driving substance use, whether substance use was driving psychological distress, or whether a bidirectional, synergistic relationship was present. The continually accruing CNICS longitudinal data will facilitate future analyses exploring these relationships. In addition, CNICS does not systematically query about all potential illicit substance use, but it does assess the most likely substances used.

We also did not determine the HIV serostatus of sexual partners, which limits estimations of HIV sexual risk behavior according to seroconcordant or serodiscordant status. Finally, it is important to note that we tested many models at the .05 significance level but that, within each domain, we fit a blocked domain-specific model that included only the other variables within the same domain, allowing us to optimize statistical power and minimize type 1 error.

The strengths of our study include the large sample size, the sample's geographic diversity, and the use of tablets to collect data, minimizing social desirability bias. Another strength was our ability to examine data on use of individual substances rather than aggregate data on substance use in general.

Conclusions

Our findings have implications for public health research, intervention, and practice. HIV medication nonadherence, HIV sexual risk behaviors, HIV disease characteristics, and psychological disorders, alongside substance use behaviors, could attenuate the public health benefits of “test, treat, and link to care” strategies,^{62,63} which are predicated on the assumption that if more HIV-infected people are tested and enrolled in care, treatment will decrease the aggregate pool of infectious viral particles in individuals and across populations (known as “community viral load”).⁶⁴⁻⁶⁶ Our results underscore the need to continue to develop and implement prevention programs that address substance use, medication nonadherence, and unprotected sex among

TABLE 4—Bivariate, Blocked, and Multivariable Model Results for Opiate Use and Injection Drug Use in the Past 3 Months: Centers for AIDS Research Network of Integrated Clinical Systems Cohort: United States, 2005–2010

Characteristic	Bivariate Models, ^a Crude OR (95% CI)	Blocked Models, ^b Adjusted OR (95% CI)	Model 1 ^c (n = 3413), Adjusted OR (95% CI)	Model 2 ^d (n = 2618), Adjusted OR (95% CI)	Model 3 ^e (n = 1292), Adjusted OR (95% CI)	Model 4 ^f (n = 656), Adjusted OR (95% CI)
Opiate use						
Demographic characteristics						
Age, y	0.98** (0.97, 0.99)	0.98** (0.97, 0.99)	0.98** (0.97, 0.99)	1.00 (0.98, 1.02)	0.97** (0.96, 0.98)	1.01 (1.00, 1.02)
Gender	0.73 (0.45, 1.18)	0.62* (0.41, 0.93)	0.66* (0.47, 0.93)	0.70 (0.31, 1.57)	0.27** (0.11, 0.65)	1.49 (0.84, 2.65)
Latino/Hispanic (vs White)	0.82 (0.73, 1.07)	0.76* (0.58, 0.99)	0.84 (0.60, 1.16)	0.58 (0.26, 1.28)	1.01 (0.45, 2.25)	0.28 (0.05, 1.48)
Black (vs White)	0.55 (0.20, 1.57)	0.49 (0.16, 1.43)	0.53 (0.20, 1.40)	0.53 (0.14, 1.97)	0.59 (0.23, 1.50)	0.58 (0.23, 1.48)
Other (vs White)	0.84 (0.30, 2.33)	0.80 (0.29, 2.22)	0.84 (0.34, 2.11)	1.15 (0.46, 2.89)	1.19 (0.26, 5.50)	1.19 (0.23, 6.03)
HIV disease characteristics and medication adherence						
Currently taking HIV medications	0.85 (0.61, 1.20)	...	1.23 (0.86, 1.76)	...	0.50* (0.28, 0.89)	1.36 (0.55, 3.38)
Detectable viral load	1.43** (1.17, 1.74)	1.21 (0.85, 1.73)	1.35* (1.05, 1.73)	1.25 (0.96, 1.63)	0.94 (0.52, 1.70)	0.94 (0.38, 2.38)
Nonadherence score	1.41** (1.26, 1.58)	1.39** (1.26, 1.53)	...	1.28** (1.07, 1.53)
Psychosocial factors						
Major depression	2.38** (1.55, 3.64)	1.67** (1.22, 2.27)	1.63** (1.18, 3.36)	1.52 (0.98, 2.34)	2.05* (1.03, 4.04)	1.69 (0.61, 4.69)
Anxiety disorder	2.33* (1.00, 5.45)	1.60 (0.68, 3.79)	1.48 (0.69, 3.18)	1.31 (0.56, 3.08)	2.68* (1.25, 5.78)	1.81* (0.18, 3.05)
Drug treatment	4.71** (3.05, 7.29)	3.93** (2.85, 5.42)	3.88** (2.57, 5.87)	4.20** (2.65, 6.68)	3.15** (1.38, 7.20)	6.08** (3.56, 10.37)
HIV sexual risk behavior						
Unprotected anal sex	1.05 (0.57, 1.92)	0.86 (0.42, 1.77)	0.58 (0.26, 1.30)	...
No. of anal sex partners	1.14** (1.07, 1.22)	1.18** (1.10, 1.26)	1.13** (1.06, 1.19)	...
Unprotected vaginal sex	0.91 (0.52, 1.59)	0.87 (0.49, 1.55)	0.65 (0.33, 1.28)
No. of vaginal sex partners	0.99 (0.86, 1.15)	1.28* (1.03, 1.60)	1.19 (0.98, 1.45)
Injection drug use						
Demographic characteristics						
Age, y	0.96** (0.95, 0.98)	0.95** (0.94, 0.97)	0.96** (0.95, 0.98)	0.96** (0.94, 0.97)	0.97** (0.95, 0.99)	...
Gender	1.66 (0.82, 3.34)	1.54 (0.59, 3.99)	1.87 (0.82, 4.29)	1.44 (0.37, 5.68)	0.61 (0.32, 1.17)	...
Latino/Hispanic (vs White)	0.82 (0.45, 1.51)	0.69 (0.36, 1.35)	0.84 (0.41, 1.71)	0.73** (0.59, 0.91)	0.99 (0.75, 1.32)	...
Black (vs White)	0.34** (0.26, 0.45)	0.28** (0.22, 0.36)	0.26** (0.16, 0.42)	0.32** (0.14, 0.73)	0.12** (0.03, 0.46)	...
Other (vs White)	0.49** (0.29, 0.82)	0.44* (0.23, 0.84)	0.51** (0.33, 0.79)	0.56 (0.13, 2.22)	1.13 (0.51, 2.51)	...
HIV disease characteristics and medication adherence						
Currently taking HIV medications	0.71 (0.49, 1.01)	...	1.05 (0.77, 1.42)	...	1.39 (0.55, 3.50)	...
Detectable viral load	1.75** (1.39, 2.19)	1.48** (1.15, 1.90)	1.36** (1.12, 1.66)	1.30** (1.07, 1.57)	1.35 (0.94, 1.94)	...
Nonadherence score	1.48** (1.31, 1.67)	1.44** (1.27, 1.63)	...	1.38** (1.18, 1.60)
Psychosocial factors						
Major depression	3.46** (2.85, 4.19)	2.19** (1.75, 2.73)	2.74** (1.96, 3.81)	2.01** (1.51, 2.69)	2.52** (1.66, 3.83)	...
Anxiety disorder	2.71** (1.64, 4.48)	1.52 (0.85, 2.72)	1.50 (0.79, 2.82)	1.42 (0.82, 2.46)	1.55 (0.85, 2.82)	...
Drug treatment	7.36** (5.65, 9.60)	5.00** (4.03, 6.20)	6.17** (4.19, 9.09)	7.22** (5.29, 9.85)	5.90** (3.04, 11.45)	...

Continued

TABLE 4—Continued

HIV sexual risk behavior						
Unprotected anal sex	4.70** (3.30, 6.69)	3.30** (1.84, 5.94)	2.45** (1.42, 4.22)	...
No. of anal sex partners	1.41** (1.28, 1.56)	1.39** (1.26, 1.54)	1.31** (1.19, 1.44)	...
Unprotected vaginal sex	0.86 (0.38, 1.93)	0.73 (0.32, 1.66)
No. of vaginal sex partners	1.01 (0.95, 1.07)	0.31** (0.19, 0.51)

Note. CI = confidence interval; OR = odds ratio. Generalized estimating equations were used to fit logit models to adjust for geographic location (the design covariate in all models was study site).

^aResults from fitted bivariate logistic regression models.

^bResults from multivariable logistic regression models examining block group baseline factors (e.g., domain-specific variables) associated with substance use.

^cIncludes all participants. Statistical predictors were age, gender, race/ethnicity, currently taking HIV medication, detectable viral load, depression, anxiety, and substance use treatment in the preceding year.

^dRestricted to participants who reported currently taking HIV medications. This model included the same variables as model 1 with the addition of medication nonadherence.

^eRestricted to participants who reported anal sex in the preceding 6 months. This model included the same variables as model 1 with the addition of unprotected anal sex and number of anal sex partners.

^fRestricted to participants who reported vaginal sex in the preceding 6 months. This model included the same variables as model 1 with the addition of unprotected vaginal sex and number of vaginal sex partners. The model was not fit for the injection drug use outcome owing to an insufficient sample size.

* $P < .05$; ** $P < .001$.

patients enrolled in primary care, which will improve virological outcomes among HIV-infected patients as well as decrease transmission to their sexual partners. ■

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Contributors

M. J. Mimiaga and K. H. Mayer originated the study. M. J. Mimiaga and S. L. Reisner analyzed the data. M. J. Mimiaga wrote the final version of the article. All of the authors interpreted findings, contributed ideas, and participated in the writing of the article.

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Human Participant Protection

This study was approved by the institutional review board at each participating site. Participants provided written informed consent.

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