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## Rates of mood and anxiety disorders and contributors to continued heroin use in methadone maintenance patients: A comparison by HIV status

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### Abstract

The frequency of mood and anxiety disorders is elevated among individuals with a history of intravenous drug abuse and among those with human immunodeficiency virus (HIV), and these disorders are associated with continued substance use despite treatment. The present study examined rates of mood and anxiety disorders, and recent heroin use, among HIV-infected and HIV-noninfected patients receiving methadone maintenance therapy. Participants were 160 (80 HIV-infected, 80 HIV-noninfected) methadone patients. Clinician-administered, semistructured interviews were used to identify unipolar and bipolar depression, and four major anxiety disorders (panic disorder with agoraphobia [PDA], generalized anxiety disorder [GAD], post-traumatic stress disorder [PTSD], and social anxiety disorder [SAD]). Toxicology screens and self-reporting were used to assess heroin, cocaine, marijuana, and alcohol use over the past month. The entire sample met criteria for at least one psychiatric disorder other than substance dependence. Substantial proportions of participants met criteria for major depressive disorder (55.6%), bipolar I, bipolar II, or cyclothymia (6.4%), PDA (34.4%), GAD (22.5%), SAD (16.9%), and PTSD (34.4%). A greater proportion of HIV-infected participants met criteria for SAD ( $\chi^2 = 5.03$ ), and a greater proportion of HIV-noninfected participants met criteria for GAD ( $\chi^2 = 5.39$ ,  $P < 0.01$ ). About 14% of participants continued to use heroin over the past month, a significantly greater proportion of whom were HIV-infected. In adjusted analyses, none of the mood or anxiety disorders emerged as significant predictors of recent heroin use, but being HIV-infected did. This study highlights the high rate of psychopathology and continued heroin use despite substance abuse treatment, and underscores the need for interventions that help mitigate these problems among methadone patients.

### Keywords

psychopathology; substance dependence; human immunodeficiency virus; methadone

### Introduction

Mood and anxiety disorders are highly comorbid with substance use disorders.<sup>1–5</sup> High rates of comorbidity may result from the desire to self-medicate against the distress associated

with anxious and depressive symptoms.<sup>6,7</sup> Individuals with diagnosed Axis I psychiatric disorders may be more sensitive to their internal anxiety states and thus more likely to use alcohol or other substances to avoid experiencing these distressing states fully.<sup>8</sup> Intravenous (IV) drug (ie, heroin) use in particular has been associated with the presence of comorbid mood and anxiety disorders.<sup>9–11</sup> For example, the lifetime prevalence for major depressive disorder (MDD) has been estimated to be 17% in the general population,<sup>12</sup> and as high as 52% among opioid users.<sup>10</sup> Furthermore, more than two-thirds (70%) of adults with opioid dependence may suffer from a mood or anxiety disorder during their lifetime.<sup>10,12</sup>

For individuals also managing the multiple stressors of human immunodeficiency virus (HIV) infection, comorbid mental health and substance use disorders substantially impact optimal disease management. There is evidence that HIV-infected patients continue to engage in more illicit drug use<sup>13,14</sup> and experience greater rates of psychiatric disorders than their HIV-noninfected counterparts.<sup>14–16</sup> It has also been suggested that HIV-infected adults with a substance use disorder are more likely to have comorbid anxiety or depression than HIV-infected adults without a substance use disorder.<sup>17</sup>

Despite high rates of IV drug use and comorbid psychiatric diagnoses among HIV-infected adults, only a few studies have investigated the relationship between psychopathology and IV drug use among HIV-infected patients,<sup>16,18,19</sup> and fewer still have compared rates of psychopathology between HIV-infected and HIV-noninfected IV drug users.<sup>20,21</sup> Although opioid substitution therapy, usually methadone maintenance therapy, remains the most common medical intervention for opioid addiction,<sup>22–24</sup> research on the relationship between these variables among patients enrolled in methadone maintenance programs is limited.<sup>25,26</sup>

The purpose of the present study was to examine rates of mood and anxiety disorders in a sample of HIV-infected and HIV-noninfected methadone patients, and to assess whether these rates vary according to HIV status. A secondary goal was to examine the rate of continued heroin use, and to gain a clearer understanding of factors (ie, psychopathology, HIV) that may contribute to continued substance use despite enrollment in substance abuse treatment. Identification of risk factors for continued IV drug use among methadone patients has public health relevance given that these individuals are at an increased risk for HIV infection or transmission.<sup>13,27</sup> IV drug use is of particular concern because it facilitates the transmission of HIV infection through contaminated injection equipment. It is estimated that 32% of women and 18% of men living with HIV in the US contracted the virus through IV drug use, and HIV infection is most frequently transmitted through the injection of heroin.<sup>28,29</sup> Heroin use is also associated with relapse among patients enrolled in methadone maintenance therapy.<sup>30</sup> Due to this increased risk of HIV transmission, and because our sample was comprised of patients enrolled in treatment for opioid dependence, we chose to focus primarily on heroin use. However, to address the study purpose more broadly, we also examined other common substances of abuse, ie, cocaine, marijuana, and alcohol, and the relationship between these variables, psychopathology, and HIV status.

## Methods

### Participants

Participants included 80 HIV-infected and 80 HIV- noninfected adults with opioid dependence who were undergoing methadone maintenance. The HIV-infected participants were part of an ongoing National Institute on Drug Abuse (NIDA)-funded project investigating cognitive behavioral therapy (CBT) for enhancing medication adherence and treating depression in individuals with HIV. The 80 HIV-noninfected individuals were recruited from the same methadone treatment centers in which the parent study was based.

Both groups (HIV-infected and HIV-noninfected) completed identical assessment protocols. The assessment protocol completed by all participants represented the baseline assessment of the parent study's design.

Inclusion criteria for the HIV-infected group were being HIV seropositive and taking HIV antiretroviral medication (without methadone), current enrollment in a methadone maintenance program, and aged 18–65 years. Inclusion criteria for the HIV-noninfected group were being HIV seronegative (by self-report), current enrollment in a methadone maintenance program, and aged 18–65 years. All participants received once-daily methadone. Participants were excluded from both study samples if they had such severe mental illness that they required immediate treatment (ie, active psychosis), were unwilling to consent, or were currently receiving CBT for depression. Although the parent study of HIV-infected patients was a trial for treating depression and adherence, all HIV-infected patients at the methadone clinics were screened for depression, and this screening data was the data source for the present analysis.

## Materials

**Diagnostic evaluation**—The Mini-International Neuropsychiatric Interview (MINI)<sup>30</sup> is a short structured diagnostic interview that has reliability and validity comparable with the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV).<sup>31</sup> The MINI was used to assess current and lifetime alcohol use, anxiety disorders, mood disorders, and psychosis. Psychometric examination of the MINI has shown acceptable test-retest and inter-rater reliability.<sup>30</sup>

**Rating of depression**—The Montgomery-Asberg Depression Rating Scale (MADRS)<sup>32</sup> is an assessment of 10 commonly occurring symptoms of depressive illness over the past week, and is a widely used and valid instrument. The MADRS appears to be a unidimensional scale oriented more towards the psychic, as opposed to somatic, aspects of depression.<sup>33</sup> Scores on the MADRS range from 0 to 60, with scores between 0 and 6 indicating no depression; scores between 7 and 19 indicating mild depression; scores between 20 and 34 indicating moderate depression; and scores between 35 and 60 indicating severe depression.

**Rating of drug use**—The Addictions Severity Index (ASI)-Lite<sup>35</sup> measures the severity of problems in seven areas of functioning that are frequently affected in patients with substance use disorders. This instrument provided information regarding the participant's history and current use of heroin, cocaine, marijuana, and alcohol, as well as other substances over the past 30 days. The ASI-Lite was administered by clinicians and required patients to report substance use during the past 30 days.

Participants provided oral toxicology swabs to screen for recent use of various substances, including opiates. Assays were run using gas chromatography-mass spectrometry analysis. This method has been validated on oral fluid samples analyzed across the five SAMHSA (Substance Abuse and Mental Health Services Administration) drug categories (ie, marijuana, cocaine, opiates, phencyclidine, and amphetamines) that examined more than 77,000 samples from workplace testing.<sup>36</sup> This procedure is consistent with SAMHSA draft guidelines for drug testing using saliva and has been generally endorsed.<sup>36,37</sup>

Dichotomous variables indicating whether patients had used heroin, cocaine, marijuana, or alcohol over the past month were used in these analyses. These variables represented the combination of self-reporting and toxicology data (except for alcohol, which was based only on self-reporting data), such that if participants self-reported “no” to heroin use over the past month, but the toxicology screen result was positive, that participant was assigned “yes”.

**Demographic questionnaire**—A basic self-report questionnaire was used to collect information about age, gender, sexual orientation, race/ethnicity, level of education, and employment status.

## Procedure

Participants were recruited through clinician referrals and advertisements at methadone treatment clinics in Massachusetts and Rhode Island, where patients receive daily methadone treatment. During their clinic mental health appointments, patients were introduced to the study by their methadone counselor or psychiatrist. For all interested patients who provided contact information, a study research assistant contacted them to explain the study in more detail, screen for initial eligibility, and schedule the baseline assessment with a study clinician.

At the baseline assessment, the clinician explained the study procedures in detail and obtained informed consent. The clinician then completed a diagnostic evaluation including an assessment of mood and anxiety symptoms and recent substance use. If suicidality or risk of harm to others was identified during the assessment, the clinician notified a licensed psychologist on the study staff and appropriate service referrals were made.

The study was reviewed and approved by the Institutional Review Boards for Massachusetts General Hospital and Rhode Island Hospital, respectively.

## Statistical analyses

Chi-square analyses were conducted to assess for differences between HIV-infected and HIV-noninfected participants on demographic variables. Similar analyses were used to evaluate variations between groups on the mental health and substance use variables. In order to examine the interrelationships between psychopathology, HIV status, and heroin use, separate logistic regression models were tested for each mood and anxiety disorder. Specifically, the mood or anxiety disorder, HIV status, and the interaction between these two factors were identified as predictors of risk for heroin use over the past 30 days. In each model, the mood or anxiety disorder (1 = meets criteria, 0 = does not meet criteria) was entered in Block 1, HIV status (1 = infected, 0 = noninfected) was entered in Block 2, and an interaction term representing the product of HIV status and the mood or anxiety disorder in Block 3. If a DSM-IV disorder was associated with continued heroin use, the order of entry in the regression equations allowed us to see if the result remained after entering HIV status, and, for the interaction, whether HIV status served as a moderator.

## Results

### Sample characteristics

Demographic characteristics of the study sample according to HIV status are presented in Table 1. Among the HIV-infected sample, approximately half of the participants were male, 51.2% identified as white and 72.5% identified as exclusively heterosexual. Similarly, approximately one half of HIV-uninfected participants were male, 61% identified as white, and 85% as exclusively heterosexual. HIV-infected participants were, on average, 44 years old and completed an average of 11 years of school, while HIV-noninfected participants were, on average, 42 years old and had completed 12 years of school. A significantly greater proportion of HIV-infected participants were on disability ( $\chi^2 [1, n = 156] = 11.50, P < 0.001$ ). There were no other significant differences in demographic variables between HIV-infected and noninfected participants. Among HIV-infected participants, the average CD4 and viral load was 401.19 (SD 252.57) and 4386.57 (SD 17001.12), respectively. Twenty-four percent of HIV-infected participants met criteria for autoimmune deficiency syndrome

(AIDS) based on a CD4 cell count of lower than 200, and 63.2% had an undetectable viral load at the baseline assessment.

### Rates of affective psychopathology

The rates of mood and anxiety disorders by HIV status are presented in Table 2. It is notable that the entire sample met criteria for at least one psychiatric disorder other than substance dependence, ie, 17.5% met criteria for one disorder, 35% for two disorders, 30% for three disorders, 13.1% for four disorders, 3.1% for five disorders, and 1.3% met criteria for six disorders. For the entire sample, 55.6% met criteria for current, chronic, or recurrent major depressive disorder (MDD), 6.4% met criteria for bipolar I, bipolar II, or cyclothymia, 34.4% met criteria for panic disorder with agoraphobia (PDA), 22.5% met criteria for generalized anxiety disorder (GAD), 16.9% met criteria for social anxiety disorder (SAD), and 34.4% met criteria for post-traumatic stress disorder (PTSD). A significantly greater proportion of HIV-noninfected participants met criteria for GAD ( $\chi^2 [1, n = 160] = 5.025, P < 0.01$ ; 31.3% versus 13.8%), and a significantly greater proportion of HIV-infected participants met criteria for SAD ( $\chi^2 [1, n = 60] = 5.391, P < 0.05$ ; 23.8% versus 10%). Other disorders did not vary by HIV status.

Among the entire sample, 13.8% of participants reported using heroin in the past 30 days. When heroin use was examined between HIV-infected and noninfected participants, the results indicated that a significantly greater proportion of HIV-infected participants used heroin over the past month ( $\chi^2 [1, n = 160] = 5.27, P < 0.05$ ; 20% of HIV-infected and 7.5% HIV-noninfected participants reported using heroin over the past month).

### HIV status, depression, anxiety, and risk of recent heroin use

The results of the logistic regression models indicated that there was no main effect for any of the mood or anxiety disorders. However, being HIV-infected predicted greater likelihood of using heroin over the past month in the context of MDD (odds ratio [OR] 3.29, 95% confidence interval [CI]: 1.2–8.9,  $P < 0.05$ ), PDA (OR 3.00, 95% CI: 1.1–8.2,  $P < 0.05$ ), GAD (OR 3.84, 95% CI: 1.34–11.03,  $P < 0.05$ ), SAD (OR 2.86, 95% CI: 1.04–7.86,  $P < 0.05$ ) and PTSD (OR 3.22, 95% CI: 1.18–8.81,  $P < 0.05$ ). HIV status did not moderate the relationship between any mood or anxiety disorder and risk of recent use of heroin. Accordingly, the interaction terms were not significant in any model.

To address the issue of continued substance use in the context of substance use treatment more broadly, we also examined the use of cocaine, marijuana, and alcohol in this sample. Nearly 38% of the entire sample reported using cocaine, 21.9% reported using marijuana, and 20% reported using alcohol over the past month. Table 3 presents descriptive data regarding the use of these substances according to HIV status. There were no significant differences between groups in the use of any of these substances. Additionally, in logistic regressions, none of the psychopathology variables, or HIV status, emerged as significant predictors of continued use of cocaine, marijuana, or alcohol over the past month.

## Discussion

The purpose of the present study was to describe the rate of psychopathology and recent heroin use in a sample of HIV-infected and HIV-noninfected methadone patients, and to evaluate the relationship between HIV status, mood and anxiety disorders, and heroin use among these patients.

There were remarkably high rates of mood and anxiety disorders among this sample of HIV-infected and HIV-noninfected methadone patients. One hundred percent of participants met criteria for at least one Axis I disorder in addition to substance dependence, and nearly one-

third of participants met criteria for two disorders. Although previous studies have reported high rates of mood and anxiety disorders,<sup>14,17,20</sup> the rate of psychopathology found in this sample is significantly higher than rates previously reported.

Over one half of the entire sample met criteria for current, chronic, or recurrent MDD, over a third met criteria for PDA or PTSD, and nearly 23% met criteria for GAD. Moreover, approximately 17% of participants met criteria for SAD and 6.4% met criteria for bipolar I, bipolar II, or cyclothymia. These rates speak to the importance of treating mental health disorders in the context of pharmacologic interventions for substance dependence, regardless of HIV status.

As noted earlier, previous studies have reported higher rates of anxiety disorders among HIV-infected than HIV-noninfected participants.<sup>14,37</sup> We replicated this finding for SAD, but found the opposite results for GAD. For GAD, rates were higher for participants who were HIV-noninfected. GAD is characterized by excessive worry, and it is possible that excessive worry may promote engagement in HIV-protective practices (ie, safer sex, using clean needles) that increase participants' likelihood of remaining negative. In contrast, SAD is characterized by excessive concern about evaluation or performance situations. This may lead to greater exposure to risk factors<sup>38,39</sup> (eg, lower rates of requesting condom use). Among HIV-infected men who have sex with men and men who have sex with women, a relationship between social anxiety and risky sexual behavior has been documented, and was shown to have been maintained after controlling for substance use, social support, depression, and communication regarding condom use.<sup>40,41</sup>

Among the entire sample of methadone maintenance patients, about 14% reported using heroin over the past 30 days, a rate comparable with previous studies.<sup>25,42</sup> None of the mood or anxiety disorders predicted use of heroin over the past month. However, there was a significant difference in the rate of recent heroin use between HIV-infected (20%) and HIV-noninfected (7.5%) participants. Furthermore, HIV-infected participants remained over three times more likely than HIV-noninfected participants to use heroin over the past month, independent of MDD, GAD, PDA, and PTSD, and nearly three times more likely to use heroin, independent of SAD.

The present findings are in accordance with previous studies showing that HIV-infected patients continue to engage in more illicit drug use<sup>13,14</sup> than their noninfected counterparts, particularly with regard to IV drug use.<sup>13,14,27,43</sup> Specifically for individuals on methadone maintenance therapy, more work is needed to determine factors that may contribute to continued heroin use among those who are HIV-infected. Studies of risk factors for recidivism in methadone treatment have focused on sociodemographic factors and unmet psychosocial needs,<sup>44,45</sup> as well as adequate methadone dosing.<sup>46</sup> Extending this work, it is possible that HIV-specific factors may lead to elevated psychosocial risk or to suboptimal methadone doses that do not adequately reduce opioid craving. For instance, some antiretroviral treatment regimens (eg, non-nucleoside reverse transcriptase inhibitors [NNRTIs]) have been shown to reduce blood concentrations of methadone and thus increase risk for opioid withdrawal effects.<sup>47</sup> Among the HIV-infected sample, 21 participants were taking NNRTI-based regimens, 53 participants were taking protease inhibitor-based regimens, and three participants were taking a combination of the two. There were no significant differences in recent heroin use between participants on NNRTI- versus protease inhibitor-based regimens, ( $\chi^2 [1, n = 69] = 0.038, P = 0.543$ ). Given the small number of participants on NNRTI-based regimens here, we may not have had adequate power to assess a relationship. By examining factors such as type of antiretroviral regimen, current methadone dose, adherence to methadone treatment, perceived level of opioid craving, and

patients' motivational status, future studies may be able to elucidate biobehavioral mechanisms of continued heroin use for individuals who are HIV-infected.

In addition to heroin use, our results also indicated that almost 38% of the entire sample reported using cocaine, 21.9% reported using marijuana, and 20% reported using alcohol over the past month. The risk of using these substances did not vary significantly according to HIV status or the presence of any of the mood or anxiety disorders. While participants may have continued to use substances in order to self-medicate against pervasive mood and anxiety symptoms, it is also possible that the high rate of comorbid psychopathology and substance use found in this sample may have obscured any variations that were anticipated given previous research.

Several limitations of this study should be noted. First, the data presented here were collected during one assessment visit. Because information regarding psychopathology and substance abuse were assessed at the same time point, we are unable to draw conclusions regarding causality between these variables. As noted previously, there is a dearth of studies examining the relationship between HIV, psychopathology, and continued substance use among methadone maintenance patients. While the present study has helped to fill this gap, the results cannot be generalized to individuals with opioid addiction who are not on methadone therapy. Additionally, a dichotomous variable indicating whether patients had used heroin over the past month was used in the analyses. This represented the combination of self-reporting and toxicology data, such that if participants self-reported "no" to heroin use over the past month, but the toxicology screen result was positive, that participant was assigned "yes". Although this variable provides us with an overall sense of the proportion of participants who used heroin over the past month despite enrollment in substance abuse treatment, it lacks specificity regarding the number of days of use over the past month.

Finally, we did not include information regarding the specific methadone dose for each participant. Studies suggest that higher doses of methadone (eg, greater than 100 mg/day) have the potential to block the euphoric effects of heroin<sup>48-50</sup> and hence, to reduce heroin use. If these data had been available, we would have been able to explore whether there were significant differences between HIV-infected and HIV-noninfected participants with regard to methadone dose. It is possible that significant variations in methadone dose may have biased the results, such that the higher rates of recent heroin use among HIV-infected participants may have been the result of lower average methadone doses, rather than HIV status.

These results underscore findings from the literature that continued mood and anxiety disorders, as well as continued IV drug use despite enrollment in substance abuse treatment programs, is common.<sup>51-55</sup> The study also confirms previous findings that HIV-infected adults are more likely to engage in IV drug use than HIV-noninfected adults. This is particularly concerning given the increased risk of HIV transmission via IV drug use, and the association between psychopathology and HIV transmission/ acquisition risk behaviors. Continued HIV testing and prevention efforts (ie, needle exchange programs), and focused psychotherapeutic interventions targeting continued substance use,<sup>56,57</sup> remain a priority, and further investigation is needed to determine if treating mental health problems in this context will augment the efficacy of such regimens in terms of substance abuse outcomes. Moreover, additional studies of HIV-infected methadone patients will allow us to understand better the factors that maintain continued heroin use.

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**Table 1**

Sociodemographic characteristics of respondents (according to HIV status)

Variable	HIV- infected (n = 80)		HIV-noninfected (n = 80)	
	n	%	n	%
Gender				
Female	42	52.5	43	53.8
Male	38	47.5	37	46.2
Hispanic/Non-Hispanic				
Hispanic or Latino	26	32.5	8	10.0
Non Hispanic/Latino	54	67.5	72	90.0
Ethnicity				
African American/Black	19	23.8	21	26.3
White	41	51.2	49	61.2
Asian	2	2.5	0	0.0
Native Hawaiian/Pacific Islander	1	1.3	0	0.0
Native American	2	2.5	2	2.5
Other	15	18.7	8	10.0
Sexual orientation				
Exclusively heterosexual	58	72.5	68	85.0
Bisexual	4	5.0	3	3.8
Exclusively homosexual	2	2.5	3	3.8
Other	16	20.0	6	7.4
Religion				
Catholic	45	56.2	41	51.2
Protestant	10	12.5	15	18.7
Jewish	1	1.3	1	1.3
Islamic	1	1.3	1	1.3
Other	23	28.7	22	27.5
Relationship status				
Married/living with someone as if married	26	32.5	32	40.0
Noncohabitating relationship	6	7.5	7	8.7
Single	33	41.3	32	40.0
Divorced/separated	8	10.0	6	7.5
Loss of long-term partner	7	8.7	3	3.8
Employment				
Full-time work/school	2	2.5	3	3.8
Part-time work/school	6	7.5	11	13.7
Neither work or in school	21	26.3	25	31.2
On disability	47	58.7	32	40.0
Other	4	5.0	9	11.3
	M	SD	M	SD
Age	43.96	6.18	41.36	10.89

Variable	HIV- infected (n = 80)		HIV-noninfected (n = 80)	
	n	%	n	%
Years of education	11.15	2.35	12.16	4

**Abbreviations:** HIV, human immunodeficiency virus; M, mean; SD, standard deviation.

**Table 2**

Rate of mood and anxiety disorders according to HIV status

Diagnostic category	HIV-infected (n = 80)		HIV-noninfected (n = 80)	
	n	%	n	%
Current, chronic, or recurrent major depressive disorder	48	60	41	51.3
Dysthymia	0	0.0	0	0.0
Bipolar I/II/cyclothymia	5	6.3	5	6.3
Panic disorder with agoraphobia	23	28.8	32	40.0
**Generalized anxiety disorder	11	13.8	25	31.3
*Social phobia	19	23.8	8	10.0
Post-traumatic stress disorder	11	13.8	15	18.8

**Notes:**\*  $P < 0.05$ ;\*\*  $P < 0.01$ .**Abbreviation:** HIV, human immunodeficiency virus.

**Table 3**

Rate of substance use according to HIV status

Substance	HIV-infected (n = 80)		HIV-noninfected (n = 80)	
	n	%	n	%
Heroin	16	20.0	6	7.5
Cocaine	25	31.3	24	30.0
Marijuana	15	8.8	21	26.3
Alcohol	17	21.3	15	8.8

**Notes:**  $P < 0.05$ ;\*\*  
 $P < 0.0$ .**Abbreviation:** HIV, human immunodeficiency virus.