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ORIGINAL ARTICLE

Medication Adherence and HIV Symptom Distress in Relation to Panic Disorder Among HIV-Positive Adults Managing Opioid Dependence

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Abstract Panic disorder (PD) occurs at greater rates among those with HIV compared to those without HIV. Rates of PD may be elevated among those with opioid dependence (persons who inject drugs, PWID). Persons with HIV experience common bodily symptoms as a result of the disease and these symptoms overlap with those of PD which may contribute to a "fear of fear" cycle present in PD. HIV-positive, PWID represent an at-risk population in terms of poor medication adherence. HIV symptoms and HIV medication side-effects commonly overlap with panic symptoms and may affect HIV medication adherence. The aim of this investigation was to examine the impact of PD on HIV-related symptom distress and HIV medication adherence in HIV-positive adults (N = 131) in treatment for opioid use. Those with a diagnosis of PD evidenced greater levels of HIV symptom distress and lower levels of medication adherence than those without current PD. Results highlight the clinical importance of assessing for and treating PD among individuals with HIV that are prescribed antiretroviral therapy. Future work would benefit from examining observed associations longitudinally and identifying potential mechanisms involved.

Keywords HIV · Panic disorder · Adherence · Distress · Substance use

Introduction

Compared to general population estimates, mood and anxiety disorders are highly prevalent and comorbid with one another among persons with HIV (Bing et al. 2001). While the study of depressive symptoms and disorders among those living with HIV has received significant theoretical and empirical attention (Ickovics et al. 2001; Leserman 2008), linking it with worse adherence to treatment and HIV outcomes, less work has been conducted examining the role of anxiety disorders in general, and panic disorder in particular.

Despite high rates panic disorder among those with HIV, there is little empirical investigation focused on how panic disorder might affect the management of HIV. Panic disorder (PD) is characterized by the misinterpretation of benign physical and cognitive sensations as serious and life-threatening (i.e., elevated heart rate, increased respiratory rate, loss of control), as well as anxious apprehension surrounding the possibility of future panic episodes (Barlow 2002). Among the general population, PD is responsible for substantial functional impairment (Kessler et al. 2006), poor quality of life (Barrera and Norton 2009), and reductions in perceived health (Gadermann et al. 2012). There are at least two clinically relevant reasons for studying PD among those with HIV. First, evidence

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suggests PD is more prevalent among those with compared to those without HIV (11–16 vs. 4–7 %, respectively; (Bing et al. 2001; Kessler et al. 2006). Second, persons with HIV experience common bodily symptoms as a result of the disease and medications used to treat HIV (Justice et al. 2001) and these symptoms significantly overlap with those of PD (e.g., dizziness, nausea) and may contribute to a "fear of fear" cycle present in PD.

PD may also play a substantial and clinically meaningful role in Antiretroviral Therapy (ART) adherence difficulties among those with HIV (Tsao et al. 2004). There is evidence suggesting a number of medical conditions are associated with high rates of PD compared to the general population including asthma (Goodwin and Eaton 2003), chronic obstructive pulmonary disease (Willgoss and Yohannes 2013), migraine (Smitherman et al. 2013), and spinal pain (Von Korff et al. 2005). Although rates of PD may be higher in certain medical conditions, little is understood as to how PD may specifically impact HIV disease management. In a nationally representative probability sample, PD was associated with greater odds (OR = 2.0) of non-adherence than non-psychiatric controls (Tucker et al. 2003). In a nationally representative sample of HIV-positive adults, PD was related to the experience of pain, after controlling for HIV disease stage (Tsao et al. 2004). It is important to further evaluate potential associations between PD and HIV symptom burden and ART adherence.

Adherence to antiretroviral therapy (ART) is a vital component of successful viral suppression, delays in clinical progression, and decreased AIDS-related deaths (Emamzadeh-Fard et al. 2012; Garcia de Olalla et al. 2002; Low-Beer et al. 2000; Paterson et al. 2000). In addition, high ART adherence can decrease the risk for developing resistance to ART (Gardner et al. 2008; Kuritzkes 2004). Moreover, ART adherence may have important secondary HIV prevention implications: effective use of ART and attaining a suppressed viral load may reduce the likelihood of transmission of the virus (Cohen et al. 2011; Del Romero et al. 2010; Donnell et al. 2010; Fisher et al. 2010).

The current study sought to evaluate PD with respect to HIV symptom distress and HIV medication adherence among patients with HIV and symptoms of depression in treatment for opioid dependence. The sample utilized for the current study is useful because the multimorbid psychiatric presentation is unfortunately common among persons living with HIV. Of note, HIV-positive drug users represent an already at-risk population in terms of poor medication adherence (Gonzalez et al. 2011, 2013; Justice et al. 2001) and individuals with substance dependence, including opioid dependence may be at elevated risk for PD (Grant et al. 2004; Martins et al. 2009). Additionally, opioid dependence has been specifically associated with poor ART adherence (Altice et al. 2010). It was hypothesized that those with a current diagnosis of PD, compared to those without current PD, would report greater HIV symptom distress and lower medication adherence, above and beyond potentially relevant demographic and clinical factors.

Method

Participants

Participants were 131 HIV-seropositive adults (53.4 % male; $M_{age} = 46.73$, $SD = 7$; see Table 1 for demographics) in treatment for opioid dependence. The majority of participants (70.3 %) were prescribed daily methadone. The racial breakdown of the sample was 42 % Caucasian, 29 % African American, 3.1 % Native American, one individual identified as Native Hawaiian/Pacific Islander and 22.1 % reported not identifying with the listed categories (i.e., "Other"). A substantial portion of the sample (30.8 %) identified their ethnicity as Hispanic/Latino. On average, participants reported 11.06 years ($SD = 3.02$) of educational attainment. Greater than two-thirds (68.8 %) of the sample had an undetectable viral load and the average CD4 t cell count was 442.82 ($SD = 254.19$).

Measures

The Miniature International Diagnostic Interview Schedule for Psychiatric Illness (MINI; Sheehan et al. 1998*)* was used to assess for current DSM-IV-TR psychological disorders, including current major depressive disorder. The MINI is a widely utilized measure of psychopathology that assesses diagnosis based on DSM-IV-TR criteria The MINI has evidenced adequate reliability and validity including concurrent validity with other diagnostic measures and is intended for lay-person administration (Sheehan et al. 1998). As part of this study, evaluation was completed by a clinical psychologist, master's level clinician, or doctoral student, and was presented for review and diagnostic consensus by the study team.

Medication-Event-Monitoring-System (MEMS; AARDEX) caps were used to assess HIV medication adherence during a period of 2 weeks. MEMS caps are an electronic monitoring cap that fits onto a standard pill bottle and records each instance of bottle opening. We used this monitoring system to evaluate adherence to the ART medication that the participants considered the most difficult to remember or the dose taken most frequently. To account for doses that participants may have taken without opening the pill cap (e.g., took out afternoon doses when they opened the pill bottle in the morning), doses were counted as taken if participants could recall specific instances when they took their medications but did not use

Table 1 Descriptive data and bivariate relationships

Variable	1	2	3	4	5	6	7	Mean (SD) or %	Observed range
1. Age	1	.16	.13	−.24**	.07	.00	−.05	46.7 (7.0)	29–61
2. Sex[a]		1	.25**	−.16	−.13	−.04	.20*	42.1	–
3. Education			1	−.19*	−.01	−.07	.03	–	–
4. Panic disorder status[b]				1	.04	.23**	−.22*	29.8	–
5. Major depression status[b]					1	.10	−.09	55.0	–
6. Symptom distress[c]						1	−.05	33.7 (14.9)	0–73
7. Medication adherence[d]							1	68.1 (28.8)	0–100

* $p < .05$, 2-tailed; ** $p < .01$, 2-tailed

[a] Coded as 0 = female and 1 = male

[b] Coded as 0 = no and 1 = yes

[c] ACTG-Symptom Distress Module (Justice et al. 2001)

[d] Medication Event Monitoring System (MEMS, AARDEX) caps

the cap. A dose was considered missed if it was not taken within a 2-h window of the designated time. The final adherence percentage represents the percent of doses taken on-time over the 2-week period, corrected for times when participants took the medication but did not use the MEMS cap. These procedures, including using a 2-week monitoring period are common for measuring HIV medication adherence (Liu et al. 2006; Safren et al. 2009; Stirratt et al. 2006).

The AIDS Clinical Trials Group Symptom Distress Scale (ACTG; Justice et al. 2001*)* was used to measure distress related to HIV symptoms. Participants rated on a 5-point Likert-type scale (*0 = I do not have this symptom to 4 = It bothers me a lot*) the extent to which each of 20 commonly experienced symptoms experienced with HIV (e.g., *muscle aches, nausea*) is bothersome. This scale has demonstrated excellent internal consistency (Cronbach $\alpha = .92$) in previous work (Justice et al. 2001). To reduce HIV-related symptom overlap with PD we removed five items that assess panic symptoms (i.e, "Fevers, chills or sweats"; "Feeling dizzy or lightheaded", "Pain, numbness or tingling in the hands or feet", "Felt nervous or anxious", and "Cough or trouble catching your breath"). The remaining 15 items demonstrated acceptable internal consistency (Cronbachs $\alpha = .73$).

Procedure

Participants were recruited from methadone clinics in the greater Boston area and through community outreach and hospital-based HIV clinics. Individuals were recruited for a study of adherence to HIV medications for adults in treatment for opioid dependency, whether or not they self-reported problems with medication adherence or depression. Inclusion criteria included being between age 18 and 65, HIV-seropositive, prescribed antiretroviral therapy for HIV, endorsed a history of injection drug use, and were currently enrolled in treatment for opioid abuse or dependence for at least 1 month. Informed consent procedures and baseline assessments were conducted over two study visits that consisted of an assessment battery, a clinical psychiatric interview, an oral toxicology screen, and blood-draw. At the first baseline visits, participants were given a MEMS cap to monitor their HIV medication adherence for a 2-week period, which they returned at the second study visit prior to randomization into one of the two study arms. Participants were compensated $50 for their time and participation. Data for the current analyses was collected from all participants completing baseline procedures for the larger randomized controlled trial prior to treatment randomization and initiation (Safren et al. 2012).

Data Analytic Strategy

Descriptive statistics were first examined for demographic and study variables. Hierarchical regression analyses were conducted with HIV symptom distress and percentage of 2-week HIV medication adherence as the criterion variables. At step 1 of each model, the main effects of age, sex, number of years of education, and a dichotomous variable for major depressive disorder (MDD) status (0 = no MDD and 1 = MDD) were entered as potential covariates. These covariates were chosen on an a priori basis because previous work indicates relations with ART adherence (Gay et al. 2011; Hinkin et al. 2004; Puskas et al. 2011; Turner et al. 2003). Specifically, we included MDD as a covariate for two reasons: (1) past work indicates depressive symptoms are associated with poor medication adherence (Gonzalez et al. 2011) and (2) over half the sample screened positive for current major depressive disorder. At step 2, a dichotomous variable for PD status (0 = no PD and 1 = PD) was entered. To assess for the specificity of relationships with respect to PD, we then separately reran the models accounting for social anxiety disorder, and generalized anxiety disorder using dichotomous variables. Due to technical problems with the electronic pill caps, ART adherence data (MEMS) was not usable for five participants, reducing the sample size for relevant analyses to $N = 126$.

Table 2 Hierarchical multiple regression analyses

	ΔR^2	*t*	β	sr^2	*p*
Dependent variable: medication adherence[a]					
Step 1	.04				
Sex[b]		1.7	.19	.03	.09
Education		−.15	−.02	<.01	.88
Age		−.88	−.09	.01	.38
Major depression status[c]		−1.29	−.12	.02	.2
Step 2	.05				
Panic disorder status[c]		−2.47	−.24	.05	.02
Dependent variable: HIV symptom distress[d]					
Step 1	.02				
Sex		−.07	−.01	<.01	.94
Education		−1.28	−.13	.01	.2
Age		−.38	−.04	<.01	.69
Major depression status		.08	.01	<.01	.99
Step 2	.04				
Panic disorder status		2.1	.2	.04	.04

sr^2 = partial correlation squared

[a] Medication Event Monitoring System (MEMS, AARDEX) caps

[b] Coded as 0 = female and 1 = male

[c] Coded as 0 = no and 1 = yes

[d] ACTG-Symptom Distress Module (Justice et al. 2001)

Results

Descriptive Data and Psychopathology

See Table 1 for correlations among theoretically relevant variables. The average 2-week HIV medication adherence for the sample was 68.12 % (*SD* = 28.8), as measured by Medication Event Monitoring System (MEMS) caps. In terms of anxiety disorders, 29.8 % of the sample evidenced a single current anxiety disorder as assessed by the MINI. Additionally, 18.3 % met criteria for two co-occurring anxiety disorders. Twenty-nine percent of the sample met criteria for a current primary diagnosis (i.e., disorder rated most severe or impairing) of PD. A total of 55 % of the sample met criteria for current major depressive disorder, 14.5 % of the sample met criteria for generalized anxiety disorder, 11.5 % met criteria for obsessive–compulsive disorder and 22.9 % met criteria for social anxiety disorder.

Hierarchical Regression Analyses

See Table 2 for regression analyses. For HIV symptom distress, the overall model accounted for 6.0 % of variance. At step 1, the control variables did not make a significant contribution to the model (R^2 = .02). At step 2, PD status accounted for an additional 4.0 % of the variance and was a significant, positive predictor of HIV symptom distress (β = .20, *p* = .04).

For medication adherence, the overall model accounted for 9.0 % of variance. At step 1, the control variables did not make a significant contribution to the model (R^2 = .04). At step 2, PD status accounted for an additional 5 % of the variance and was a significant, negative predictor of medication adherence (β = −.24, *p* = .02).

In follow-up analyses, the relationship between PD and HIV symptom distress and medication adherence remained significant after controlling for social anxiety disorder and generalized anxiety disorder independently, in separate models.

Discussion

This is the first study, of which we are aware, showing that current PD diagnosis is associated with greater HIV symptom distress and reduced ART medication adherence in adults with HIV managing opioid dependence. These associations were observed after accounting for a current major depression diagnosis, as well as two other prevalent anxiety disorders: social anxiety disorder and generalized anxiety disorder.

Elevated rates of PD among individuals with HIV (Bing et al. 2001) and those with opioid dependence have been documented (Martins et al. 2009). In line with past findings, the prevalence of current PD was markedly high in this sample, with 29 % of participants positively assessed for a current, primary diagnosis of PD; a figure approximately tenfold higher than that documented in the general population (Kessler et al. 2005a). Negative effects of PD on social and occupational functioning have been established in the general population (Kessler et al. 2005b). However, little is known about the effects of PD on living with and managing HIV and opioid dependence. The current results build on this previous work (Gonzalez et al. 2012) and indicate a potentially unique role for PD in HIV symptom distress and medication adherence in this multiply challenged sample.

Only recently has research begun to explicate potential cognitive mechanisms between PD and HIV. Cognitive factors implicated in PD such as anxiety sensitivity may play a contributing role in the observed relationships. Anxiety sensitivity, conceptualized as the fear of anxiety-related sensations, is an established cognitive risk and maintenance factor for PD (Ehlers 1995) and is associated with HIV-symptom distress (Gonzalez et al. 2012). In addition, Gonzalez et al. (2012) found that HIV symptom distress is related to PD symptoms in the context of elevated anxiety sensitivity. Specifically, side effects of HIV and medications used to treat the virus commonly overlap

with panic symptoms. Those with PD or elevated AS may be particularly at risk for misinterpreting HIV symptoms or symptoms of opioid withdrawal as anxiety provoking, resulting in both increased anxiety-related symptom distress and poor medication adherence in an effort to avoid distressing medication-related side effects.

Although limited work has documented elevated rates of PD among individuals with opioid dependence (Gros et al. 2013), research is needed to examine potential underlying mechanisms of this relation, such as the role of acute opioid withdrawal and cognitive vulnerability factors (i.e., AS) as noted previously. Initial work supports a relation between opioid use and elevated AS (Lejuez et al. 2006). Of note, the majority of individuals in the current sample were receiving treatment(s) to maintain abstinence, which may reduce the impact of acute opioid withdrawal symptoms on observed associations. In addition, we have made efforts to account for variables of theoretical and empirical relevance in the models presented but it is plausible that additional factors unique to opioid dependence treatment may be contributing to the observed relationships (e.g., side effects of methadone treatment). Thus, the current findings should be viewed within this context. Future work would benefit from assessing observed relationships at multiple times during the course of opioid treatment (i.e., initiation, dropout).

Further investigations are warranted to parse apart observed relationships and elucidate directionality of these findings. Specifically, the analyses presented here are cross-sectional in nature; therefore neither causality nor directionality of the relationships can be determined. Future research would benefit from examining these associations longitudinally, by manipulating the variables of interest (i.e., treating PD) to evaluate the potential secondary effects on HIV specific distress and adherence or as mediators of treatment outcome, and assessing panic attack history and frequency. Although we attempted to account for the potential influence of major depressive disorder, the effects of major depression or subsyndromal depression cannot be completely ignored. In particular, depression severity and history was not explored.

The measure of HIV symptom distress was modified for these analyses to reduce the risk of construct overlap with PD but resulted in lower internal consistency relative to previous studies (Marc et al. 2012). Lastly, PD accounted for a statistically significant effect, though the portion of overall variance in HIV symptom distress and medication adherence was modest. It will be important to replicate analyses in broader samples of HIV-positive adults, including those not managing opioid use and to investigate other factors that might reduce adherence (e.g., neurocognitive deficits; Zogg et al. 2012).

The results presented here provide incremental evidence for specific and clinically important effects of PD in individuals with multiple competing and chronic psychological and physical health conditions. These results underscore the impact and importance of assessing for and treating PD in persons with HIV managing opioid use and point to the importance of developing flexible treatment platforms capable of addressing multiple comorbid mental health problems in this patient group.

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Conflict of Interest Jesse D. Kosiba, Adam Gonzalez, Conall O'Cleirigh and Steven A. Safren declare that they have no conflict of interest.

Informed Consent All study participants provided written informed consent. Enrollment occurred between July of 2005 and October of 2008. All study procedures were approved by the Institutional Review Boards at Massachusetts General Hospital (MGH) in Boston, MA and at Rhode Island Hospital in Providence, RI.

Animal Rights No animal studies were carried out by the authors for this article.

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