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HIV Medication Adherence and HIV Symptom Severity: The Roles of Sleep Quality and Memory

Kimberly A. Babson, PhD,[1,2] Adrienne J. Heinz, PhD,[1,2] and Marcel O. Bonn-Miller, PhD[1,3–5]

Abstract

The purpose of the current study was to examine the extent to which self-reported sleep quality, a clinically malleable factor, is associated with both HIV medication adherence and self-reported HIV symptom severity. In addition, we sought to examine whether sleep quality may explain the association between HIV medication adherence and symptom severity, as well as the role of self-reported memory functioning in terms of the above relations. This study took place from April 2010 to March 2012. Participants were 129 HIV-positive individuals who completed an ART pill count and series of structured clinical interviews and self-report questionnaires on sleep, memory, and HIV symptom severity. A series of regressions were conducted to test study hypotheses. After accounting for covariates (i.e., problematic alcohol, nicotine, and cannabis use, and mood disorder diagnosis), results indicated that self-reported sleep quality was associated with HIV medication adherence and self-reported HIV symptom severity, and that sleep quality partially mediated the relation between medication adherence and self-reported HIV symptom severity. In addition, memory functioning moderated the relation between self-reported sleep quality and HIV symptom severity, such that the interaction of poor sleep quality and relatively good memory functioning was associated with heightened self-reported HIV symptom severity. This study highlights the importance of assessing sleep and memory among HIV-infected individuals as they may represent treatment targets for those experiencing poor medication adherence or particularly severe HIV symptoms. Such information could lead to the inclusion of adjunct brief interventions to target sleep and memory functioning in order to reduce symptom severity among HIV-positive individuals with poor medication adherence.

Introduction

The introduction of antiretroviral therapy (ART) for the management of human immunodeficiency virus (HIV) has resulted in improved treatment of HIV, including suppression of viral load to nondetectable levels,[1] reductions in hospitalizations,[2] and mortality rates.[3,4] Indeed, individuals complying optimally with ART treatment, with an undetectable viral load and CD4 (+) count greater than 500 cells/μL, evidenced no increased risk for mortality compared to the general population.[5] ART offers significantly improved management of symptoms, though importantly, these benefits are dependent on adherence to a complex medication regimen.[6] Indeed, research has demonstrated that individuals must maintain 95% compliance to medications in order to obtain benefit.[6] Adherence rates below 95% have been shown to result in treatment failure as indicated by increases in viral load, development of drug-resistant strains of HIV, and accelerated disease progression.[6,7] Although recent medication advances (i.e., PI-boosted and NNRTI-based ART regimens) may allow for positive outcomes among those with adherence below 95%,[8] given the well-established relation between poor medication adherence and HIV symptom severity and other related negative outcomes, a continued focus on addressing adherence is necessary.[7] For this reason, it is critical to identify malleable person-level factors that can be targeted through interventions to increase medication adherence, reduce HIV symptoms, and ultimately enhance quality of life among HIV positive individuals.

Sleep disturbance is one such malleable factor, which is common among individuals with HIV across the course of the disease process.[9] In fact, up to 73% of HIV-positive

[1]Center for Innovation to Implementation and [3]National Center for PTSD, VA Palo Alto Health Care System, Menlo Park, California.
[2]Department of Psychiatry and Behavioral Sciences, Stanford School of Medicine, Stanford, California.
[4]Center of Excellence in Substance Abuse Treatment and Education, Philadelphia VA Medical Center, Philadelphia, Pennsylvania.
[5]Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania.

individuals report significant sleep disturbance,[10] thus rendering poor sleep as one of the most prevalent and debilitating HIV symptoms in both intensity and severity.[11,12] In addition to daytime fatigue, a breadth of research has demonstrated that disturbed sleep, among individuals with HIV, is associated with non-adherence to ART,[13–15] increased disease progression,[16,17] and decreased immune functioning,[18] both pre- and post-modern ART era.[10–15] For example, Gay and colleagues[13] found that among a sample of 350 participants with HIV, trouble sleeping was the symptom most strongly associated with non-adherence to ART. In addition, previous research has demonstrated that poor sleep quality is associated with self-reported HIV symptom severity among adults with HIV,[17] and lower numbers of CD3+/CD4+ cells.[18] As such, sleep disturbance may be associated with both HIV medication adherence and self-reported HIV symptom severity. In addition, it is likely that sleep quality may partially account for the relation between poor medication adherence and HIV symptom severity, as medication non-adherence has been associated with poor sleep quality,[13] while poor sleep quality has been associated with elevated HIV symptom severity.[17] In accordance, we hypothesized that poor self-reported sleep quality would be associated with HIV medication non-adherence, as well as elevated self-reported HIV symptom severity, specifically cognitive (e.g., trouble focusing, difficulty problem solving), psychological (e.g., anxious, depressed), and physical (e.g., fever, nausea, muscle pain) symptoms associated with HIV. Additionally, it was hypothesized that the already established association between HIV medication adherence and symptom severity[13] would be explained (i.e., mediated), at least partially, by deficits in self-reported sleep quality.

The Moderating role of memory

There is compelling evidence to suggest that reduced memory functioning, an established correlate of sleep quality and HIV infection,[19–21] may moderate the relation between self-reported sleep quality on both HIV medication adherence and HIV symptom severity. Of note, empirical and epidemiological work has demonstrated that sleep loss is associated with significant deficits in speed of responding, attention, vigilance, motor performance, social cognition, short term memory, memory functioning, and executive functioning (e.g., working memory, problem solving) among healthy individuals.[20] In fact, the level of functioning of a sleep-deprived individual is comparable to the 9th percentile of functioning for a fully-rested individual.[22] HIV infection also increases risk for compromised neurocognitive functioning, including poor memory functioning.[19,21] For example, research has demonstrated that HIV-positive women perform significantly worse on neuropsychological measures of verbal episodic, working, and visual memory compared to HIV-negative women. In addition, hippocampal dysfunction was noted both during encoding and retrieval of information among women with HIV in comparison to those without.[23]

Importantly, self-reported cognitive and memory difficulties are associated with greater HIV symptom severity,[24,25] lower self-efficacy for medication management,[26] decline in instrumental activities of daily living,[27] and lower self-reported quality of life[25] among individuals with HIV. Accordingly, given that (a) HIV infection and poor sleep quality have been shown independently to have a negative association with memory functioning and (b) that reduced memory functioning is associated with greater HIV symptom severity, we hypothesized that perceived everyday memory functioning may help to further elucidate (i.e., moderate) the association between sleep quality and HIV medication adherence and HIV symptom severity.

We expected to observe the above-noted associations after accounting for problematic alcohol, nicotine, and cannabis use, and mood disorder diagnosis (i.e., current depression or dysthymia). Alcohol and nicotine were included as these factors have been strongly associated with HIV medication adherence as well as symptom severity.[28–31] Cannabis use was also included as a covariate due to the method of sampling for cannabis use for the parent study (see Method section below for details). Mood disorder diagnostic status was included, as this has been associated with medication adherence, HIV symptom severity, sleep disturbances, and memory functioning.[32–37]

Methods

Participants

Participants were recruited for a study on substance use and HIV via flyers placed throughout VA medical centers and community outpatient HIV clinics in the San Francisco Bay area from April 2010 to March 2012.[38] A total sample of 180 HIV positive individuals (39 female; $M_{age}=48.21$ years, SD = 8.61) completed the study. From this parent study, a sample of 129 HIV-positive individuals (28 female; $M_{age}=$ 48.34 years, SD = 8.25) were drawn who had complete data for all measures used in the current study. The current sample did not differ from the parent sample in terms of key constructs including: medication adherence ($t=-0.27$, $p>0.05$), cigarette use ($t=-1.56$, $p>0.05$), alcohol use ($t=-1.58$, $p>0.05$), self-reported memory functioning ($t=-.47$, $p>0.05$), self-reported sleep quality ($t=1.89$, $p>0.05$), self-reported HIV symptom severity ($t=1.27$, $p>0.05$), or cannabis use status ($\chi^2=1.73$, $p>0.05$). In terms of ethnicity, 41.9% of participants identified as Black/Non-Hispanic, 30.2% as Caucasian, 10.9% as Hispanic, 10.1% as Black/Hispanic, 0.8% as Asian, and 6.2% as "Other." The majority of the sample was never married (48.4%), followed by married (20.6%), divorced (13.5%), separated (11.1%), and widowed (6.3%). In terms of education, 16.8% of participants did not finish high school, 20% graduated high school, 35.2% had some college and the remainder of the sample reported completion of a 2-year degree or higher (28.0%). On average individuals had a diagnosis of HIV for 14.43 years (SD = 7.95). For study inclusion, participants had to be (1) HIV positive; (2) currently prescribed at least one antiretroviral medication, and (3) undergoing treatment at an outpatient HIV treatment clinic. In addition, due to inclusion criteria necessary for the parent study, one-third of participants met DSM-IV criteria for cannabis dependence (with the inclusion of withdrawal), one-third were nondependent current cannabis users (use within the past 30 days), and one-third of participants were non-cannabis users (no use in the past 6 months). As a result of these inclusion criteria, cannabis use status (dependent, nondependent user, no use) was included in analyses as a covariate.

Measures

Antiretroviral medication adherence. Antiretroviral medication adherence was assessed objectively using a Pill Count Tracking Form (PCTF). The PCTF is designed to track (a) the number of each individual's ART medications, (b) the number of pills each individual should have remaining (based on pharmacy record or the previous count), and (c) the number of extra pills present since their last pharmacy refill.[39] The pill count adherence rate was calculated as the number of doses taken divided by the number expected to be taken as prescribed. This yielded an overall percentage of each individual's adherence to all ART medications.[40] All PCTF's were completed by the study project coordinator with assistance from the participant. On average, 19.28 days (SD = 19.41) elapsed between the pickup of medications at the pharmacy and the completion of the PCTF. The PCTF has been shown to be a valid and reliable assessment of medication adherence.[41]

HIV symptom severity. HIV symptom severity was assessed using The Health Status Questionnaire [HSQ[42]]. The HSQ is a 43-item measure developed by the AIDS Clinical Trials Group to assess health status and outcomes for HIV and AIDS patients.[42] The HSQ assesses general health and energy, as well as social, physical, and cognitive functioning. The HSQ also assesses 20 common HIV symptoms/ART side effects (e.g., fatigue, physical symptoms, mood disturbance) experienced in the past 4 weeks on a 5-point Likert-type scale (0 = *"I do not have this symptom"* to 4 = *"I have this symptom and it bothers me a lot"*). Within the present study, similar to prior work,[43] we do not differentiate between HIV symptoms and ART side effects due to their significant overlap. Additionally, the single item assessing sleep impairment was removed in order to decrease overlap with our sleep measure. Therefore, a total score was used to index the frequency/severity of 19 self-reported HIV symptoms/ART side effects (sleep removed), with lower scores suggesting a relative absence of symptoms/side effects. The HSQ has shown good psychometric properties[42] and internal consistency in the current sample was $\alpha = 0.91$.

Sleep quality. Subjective sleep quality was measured using a single item from the Pittsburgh Sleep Quality Index [PSQI[44]]. Specifically, we asked the following question: "*During the past month, how would you rate your sleep quality overall?"* Respondents provided answers on a scale from 0 ("*very good*") to 3 ("*very bad*"), with higher scores representing worse sleep. The subjective sleep quality component score has been shown to be a robust predictor of outcomes across samples.[45,46]

Memory functioning. Memory functioning was assessed using the Everyday Memory Questionnaire [EMQ[47,48]]. The EMQ is a 27-item self-report measure that describes memory functioning related to a number of common daily activities. Using a 9-point Likert-Type scale, participants rate the frequency with which they experience each event (1 = "*Not at all in the last 6 months*," 5 = "*More than once a month, but less than once a week*," 9 = "*More than once a day*"). Example events include "forgotten you were told something and had to be reminded," and "repeated to someone what you had just told them." The EMQ is comprised of five subscales (retrieval, task-monitoring, conversational monitoring, spatial memory, memory for activities) which can be summed to generate a total memory functioning score, with higher scores reflecting a higher frequency of memory problems. Cronbach's alpha for the current study = 0.92.

Problematic alcohol use. Problematic alcohol use was assessed using The Alcohol Use Disorder Identification Test [AUDIT[49]]. The AUDIT is a 10-item self-report measure used to assess problematic alcohol use within the past year. Responses were summed to generate a continuous index of problematic alcohol use, which was included as a covariate. Possible scores can range from 0–40 with a score of 8 indicative of clinical levels of problematic use. In the present sample Cronbach's alpha = 0.88.

Nicotine use. Nicotine dependence was assessed using the Fagerström Test for Nicotine Dependence [FTND[50]]. The FTND is a 7-item questionnaire used to assess level of dependence to nicotine. A sum score of the 7 items was used to index nicotine dependence. Participants who did not report smoking were assigned a value of zero. Level of nicotine dependence was included as a covariate in all analyses.

Cannabis use. Cannabis dependence was determined using the Structured Clinical Interview-Non-Patient Version for DSM-IV [SCID-I-N/P[51]]. The SCID-I-N/P was administered by trained research staff to determine categorical diagnostic status regarding cannabis use as follows: (a) non-use, (b) nondependent, or (c) cannabis dependent. Diagnoses were confirmed by the last author following review of recorded interviews. Cannabis use diagnosis was included as a covariate in all analyses. Cannabis use was assessed via categorical diagnoses due to hypotheses from the parent study.

Mood disorder diagnosis. Mood disorder diagnostic status was determined using the Structured Clinical Interview-Non-Patient Version for DSM-IV [SCID-I-N/P[51]]. The SCID-I-N/P was administered by trained research staff to determine categorical (present or absent) diagnostic status of current mood disorder including major depressive disorder and dysthymia. Mood disorder diagnostic status was included as a covariate in all analyses.

Procedure

Participants were recruited via flyers placed throughout a large VA Medical Center and a number of community outpatient HIV clinics throughout the San Francisco Bay area. Individuals responding to the flyers contacted the research team by phone and were provided a detailed overview of the study and screened for initial inclusionary/exclusionary criteria. Those meeting initial eligibility criteria were scheduled for a laboratory appointment. Individuals were instructed to bring all of their medications to this appointment. Upon arrival to the laboratory individuals provided written informed consent to participant and were administered the SCID I-N/P[51] by trained interviewers to further assess exclusionary and inclusionary criteria. If deemed eligible, participants then completed the above-described measures. All study procedures were approved by the Stanford University Institutional Review Board (IRB) and Mills Peninsula IRB.

Data analytic approach

Prior to data analysis, relations between continuous factors were examined using bivariate correlations (Table 1). Analyses of covariance (ANCOVA) were conducted to examine relations between categorical (cannabis status) and continuous variables, while *t*-tests were employed to examine the relations between dichotomous (mood disorder) and continuous variables.

To test the hypothesis that self-reported sleep quality would be associated with both HIV medication adherence and self-reported HIV symptom severity, we conducted two separate hierarchical multiple regressions (HMR) to examine the relation between self-reported sleep quality and HIV medication adherence, and self-reported HIV symptom severity. Next, a series of HMR's were conducted in order to examine self-reported sleep quality as a mediator of the relation between HIV medication adherence and self-reported HIV symptom severity, consistent with recommendations from Baron and Kenny.[52] A Sobel test was then conducted as a test of significance.[53]

So as to determine the moderating roles of self-reported memory functioning in terms of the above relations, two separate HMR's were conducted in order to examine self-reported memory functioning as a moderator of the relation between (1) sleep quality and HIV medication adherence, and (2) sleep quality and self-reported HIV symptom severity. For all moderation analyses, variables were standardized prior to entry into the analysis. Step 1 included covariates, Step 2 was comprised of main effects (i.e., self-reported sleep quality and self-reported memory functioning), while the interaction term (sleep X memory) was entered at Step 3. In the case of a significant interaction, post-hoc slope analyses were conducted to investigate the nature of the interaction.[54] Finally, a test of moderated mediation was conducted in order to examine the role of self-reported memory functioning in moderating the relation between self-reported sleep quality and HIV symptom severity within the context of the hypothesized sleep-mediated pathway between HIV medication adherence and symptom severity. Moderated mediation is a well-established approach for examining mediated relations that are contingent on specific levels of a moderator; therefore, the MODMED Macro (version 3.1) for SPSS was employed.[55] A regions of significance test using the Johnson-Neyman technique was used to probe the moderated indirect effect. This method estimates values of the moderator for which the indirect effect transitions from significant ($p < 0.05$) to non-significant.

Due to the established relations between substance use and HIV medication adherence and HIV symptoms, problematic alcohol, nicotine, and cannabis use, and mood disorder diagnosis were included as covariates in all analyses.[32,33,36–38,56,57]

Results

Descriptive statistics

Higher self-reported sleep quality (lower scores) was associated with better HIV medication adherence and lower HIV symptom severity, while lower HIV symptom severity was associated with better HIV medication adherence. Better self-reported memory functioning (lower scores) was associated with both better self-reported sleep quality (lower scores) and worse HIV symptom severity (Table 1). Analyses of covariance (ANCOVA) were conducted to examine relations between categorical (cannabis status) and continuous variables. Results indicated that cannabis status was significantly associated with HIV medication adherence, $F = 4.45$, $p < 0.01$, self-reported HIV symptom severity, $F = 3.88$, $p < 0.05$, self-reported sleep quality, $F = 3.29$, $p < 0.05$, and problematic alcohol use, $F = 5.56$, $p < 0.01$. Post hoc tests indicated that individuals with cannabis dependence had the greatest levels of medication nonadherence, HIV symptom severity, and sleep problems, compared to non-users ($p < 0.05$) and nondependent users ($p < 0.05$). In relation to problematic alcohol use, individuals with cannabis dependence had greater problematic alcohol use compared to non-users ($p < 0.05$), but there was no difference in comparison to nondependent users ($p > 0.05$). *T*-tests were conducted to examine the associations between dichotomous variables (i.e., mood disorder diagnostic status) and continuous variables. Results indicated that individuals with a mood disorder reported greater HIV symptom severity ($t = -5.25$, $p < 0.001$), poorer sleep quality ($t = -2.99$, $p < 0.001$), poorer memory functioning ($t = -6.84$, $p < 0.001$), and greater cigarette use ($t = -2.14$, $p < 0.05$).

Self-reported sleep quality

After accounting for alcohol and nicotine use, as well as cannabis status, self-reported sleep quality was associated with both HIV medication adherence and self-reported HIV symptom severity such that individuals with poorer self-reported

Table 1. Bivariate Correlations Among Continuous Variables

		Mean	*SD*	*Min-Max*	*1*	*2*	*3*	*4*	*5*	*6*
1	Adherence	0.81	0.27	70–100%	–	–	–	–	–	–
2	HIV symptoms	30.12	16.51	0–71	−0.21*	–	–	–	–	–
3	Sleep quality	1.33	0.86	0–3	−0.21*	0.46**	–	–	–	–
4	Memory	77.08	44.98	28–216	−0.15	0.50**	0.35**	–	–	–
5	Alcohol	7.85	8.17	0–36	−0.03	0.22*	0.02	0.21*	–	–
6	Nicotine	1.26	1.78	0–9	0.11	0.06	−0.04	0.11	0.09	–

Adherence, HIV Medication Adherence as determine by pill count[39]; Alcohol, Total problematic alcohol use [AUDIT[49]]; HIV Symptoms, self-reported HIV symptom severity with the sleep item removed[42]; Memory, Memory Functioning [EMQ[47]]; Sleep Quality, Self-reported Sleep Quality [PSQI[44]]; Nicotine, Level of nicotine dependence [FTND[50]]. For sleep quality and memory functioning, lower scores represent better sleep and memory, while higher scores represent worse sleep and memory.

*$p < 0.05$; **$p < 0.001$.

Table 2. The Relation Between Self-Reported Sleep Quality and Both HIV Medication Adherence and Self-Reported HIV Symptom Severity

Step	*Variable*	ΔR^2	R^2	β	*t*	sr^2	p
Dependent variable: HIV medication adherence							
Step 1		0.03	0.03				0.51
	Alcohol			−0.02	−0.26	0.00	0.79
	Nicotine			0.13	1.47	0.01	0.14
	Cannabis			−0.04	−0.47	0.00	0.64
	Mood			−0.10	−1.14	0.01	0.25
Step 2		0.03	0.06				0.03
	Sleep quality			−0.19	−2.13	0.03	0.03
Dependent variable: Self-reported HIV symptom severity							
Step 1		0.22	0.22				0.00
	Alcohol			0.16	1.90	0.02	0.06
	Nicotine			−0.05	−0.56	0.00	0.56
	Cannabis			0.09	1.10	0.00	0.27
	Mood			0.41	5.00	0.16	0.00
Step 2		0.14	0.35				0.00
	Sleep quality			0.38	5.06	0.14	0.00

ΔR^2, change in R^2; β, Beta; sr^2, squared semi-partial correlation.

sleep quality evidenced poorer HIV medication adherence and elevated self-reported HIV symptom severity (Table 2).

Figure 1 provides a graphical depiction of the mediation analysis. After controlling for covariates, results demonstrated that poor HIV medication adherence was associated with more severe self-reported HIV symptoms (Path C), $B = -9.99$; F (1,123) = 4.16, $p < 0.05$, and poor self-reported sleep quality (mediator, Path A), $B = -0.59$; F (1,123) = 4.52, $p < 0.05$. Examination of Path B indicated that poor sleep quality was associated with elevated self-reported HIV symptom severity, $B = 7.33$; F (1,123) = 25.64, $p < 0.01$. Finally, examination of the full model (Path C′) indicated that when self-reported sleep quality was included within the model, HIV mediation adherence was no longer associated with self-reported HIV symptom severity, $B = -5.88$; F (1,123) = 13.70, $p > 0.05$, indicating partial mediation. A Sobel test confirmed a significant partial mediation model ($Z = -1.90$, $p < 0.05$).[53]

Memory functioning

In terms of HIV medication adherence, results revealed a nonsignificant main effect for memory and a nonsignificant interaction between self-reported sleep and memory. However, a significant main effect for memory and a significant interaction between memory and self-reported sleep quality was observed for HIV symptom severity, after accounting for covariates (Table 3). Consistent with recommendations, we conducted slope analyses (±1 SD) to examine the nature of the interaction. Results demonstrated that the relation between self-reported sleep quality and memory functioning was significant for those with good self-reported memory, $\beta = 0.52$, $p < 0.01$. As shown in Fig. 2, self-reported sleep quality differentially related to HIV symptom severity as a function of self-reported memory functioning. Indeed, for individuals with poor self-reported memory functioning, sleep quality was not associated with self-reported HIV symptom severity. However, for those with relatively good memory functioning, individuals with poor sleep quality had levels of self-reported HIV symptom severity similar to those individuals with poor memory functioning.

In terms of the moderated mediation analysis to determine the role of memory functioning on the observed sleep-mediated association between HIV adherence and symptom severity, results indicated that after accounting for covariates, a significant interaction emerged between self-reported sleep quality (mediator) and self-reported memory functioning (moderator) in terms of HIV symptom severity (DV), $B = -0.08$, $t = -2.87$, $p < 0.01$, indicating a significant moderated mediation model (Fig. 1). This suggests that self-reported memory functioning affects the mediated pathway between self-reported sleep quality and HIV symptom severity.

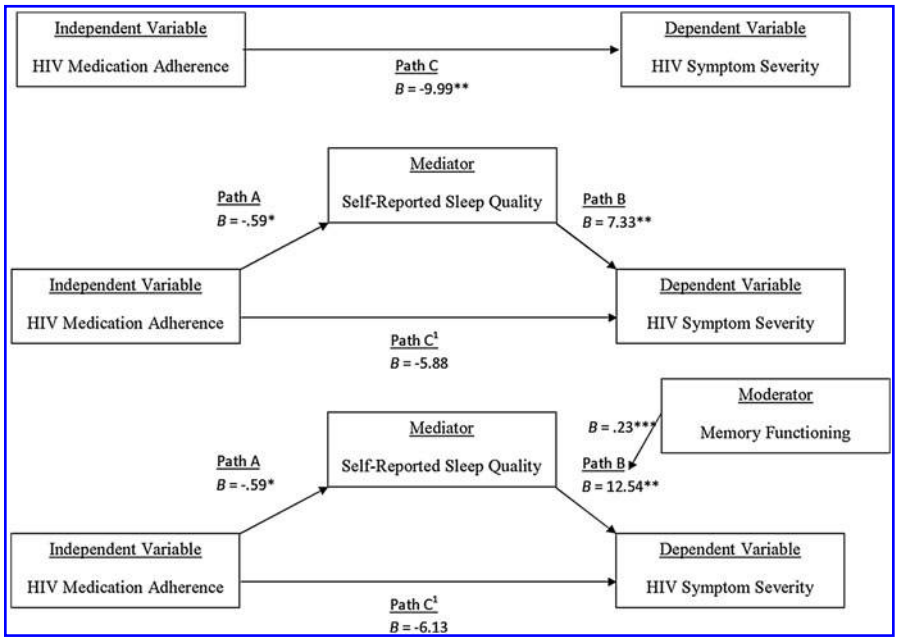

FIG. 1. Results from the mediation hypotheses. First, self-reported sleep quality as a mediator of the relation between HIV medication adherence and self-reported memory functioning is illustrated. Second, self-reported sleep quality as a mediator of the relation between HIV medication adherence and self-reported HIV symptom severity, including the moderating role of self-reported memory functioning on the self-reported sleep-HIV symptom relation, is illustrated.

Table 3. The Moderating Role of Self-Reported Memory Functioning on the Relations Between Self-Reported Sleep Quality and Both HIV Medication Adherence and Self-Reported HIV Symptom Severity

Step	*Variable*	ΔR^2	R^2	β	t	sr^2	p
Dependent variable: HIV medication adherence							
Step 1		0.02	0.02				0.51
	Alcohol			−0.02	−0.26	0.00	0.79
	Nicotine			0.13	1.47	0.01	0.14
	Cannabis			−0.04	−0.47	0.00	0.64
	Mood			−0.10	−1.14	0.01	0.25
Step 2		0.04	0.06				0.08
	Sleep quality			−0.17	−1.83	0.02	0.07
	Memory			−0.08	−0.80	0.00	0.42
Step 3		0.01	0.07				0.30
	Interaction			−0.10	−1.03	0.00	0.30
Dependent variable: Self-reported HIV symptom severity							
Step 1		0.21	0.21				0.00
	Alcohol			0.16	1.90	0.02	0.06
	Nicotine			−0.05	−0.58	0.00	0.56
	Cannabis			0.09	1.10	0.00	0.27
	Mood			0.40	5.00	0.15	0.00
Step 2		0.17	0.39				0.00
	Sleep quality			0.32	4.23	0.08	0.00
	Memory			0.26	2.93	0.04	0.00
Step 3		0.03	0.43				0.00
	Interaction			−0.21	−2.74	0.03	0.00

ΔR^2, change in R^2; β, Beta; sr^2, squared semi-partial correlation; Interaction, Self-reported sleep quality X self-reported memory functioning.

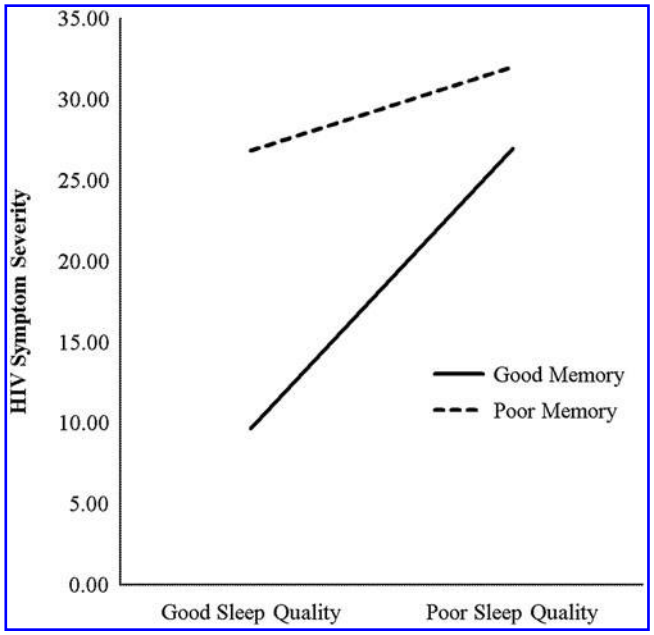

FIG. 2. Self-reported memory functioning as a moderator of the relation between self-reported sleep quality and self-reported HIV symptom severity. Simple slope analyses are represented for ± 1 SD.

Consistent with recommendations for probing significant interactions within moderated mediation models,[58] a regions of significance test using the Johnson-Neyman technique was implemented to examine the nature of the mediated relation at varying levels of the moderator including (a) the mean, (b) 1 SD above the mean, and (c) 1 SD below the mean. Results demonstrated that the effect of self-reported sleep quality on self-reported HIV symptom severity was relatively strong for those with good self-reported memory functioning (-1 SD = 32.09), $z = -1.9$; $p < 0.05$. In comparison, the relation was relatively weak for those with average ($M = 77.08$), $z = -1.87$; $p > 0.05$, or severe decrements in self-reported memory functioning (+1 SD = 122.06), $z = -1.06$; $p > 0.05$. Therefore, among individuals with low self-reported problems with memory functioning (i.e., a score lower than 77 on the EMQ[47,48]), poor self-reported sleep quality was associated with self-reported HIV symptom severity. In contrast, for individuals with average functioning to severe decrements in self-reported memory functioning [i.e., a score greater than 88.64 (scores range from 9 to 243) on the EMQ[47,48]], self-reported sleep quality had no significant association with self-reported HIV symptom severity.

In order to account for testing mediation within a cross-sectional model, and as a test of specificity,[59] we conducted a moderated mediation analysis after switching the mediator (self-reported sleep quality) and outcome (self-reported HIV symptom severity). This model therefore examined the role of self-reported HIV symptom severity as a mediator of the relation between HIV medication adherence and self-reported sleep quality while also examining the moderating role of self-reported memory functioning on this relation. Consistent with expectation, this resulted in a null model, $B = -0.00$, $p > 0.05$. This finding further improves our confidence in the direction of our observed effects, as mediation was not found when the mediator and outcome were reversed.

Discussion

The purpose of the present study was to understand the extent to which two clinically malleable factors are associated with HIV medication adherence and self-reported HIV symptom severity. First, we examined the relation between self-reported sleep quality and both HIV medication adherence and HIV symptom severity, including investigating the potential mediating role of sleep quality on the relation between HIV medication adherence and self-reported HIV symptom severity. Building from this, we then examined self-reported memory functioning as a moderator of the above-mentioned hypothesized associations. Results were partially consistent with hypotheses, as described below.

As predicted, and consistent with previous research, self-reported sleep quality was associated with both HIV medication adherence and self-reported HIV symptom severity.[13,17] Here, poor sleep quality was associated with poor HIV medication adherence and elevated self-reported HIV symptom severity after accounting for alcohol and nicotine use, as well as cannabis status. In addition, self-reported sleep quality partially mediated the observed and replicated relation between HIV medication adherence and self-reported HIV symptom severity.[13] Specifically, the observed association between medication adherence and HIV symptom

severity was, at least partially, explained by self-reported sleep quality. These results provide initial data to suggest that sleep quality may be involved in a "forward-feeding" cycle, such that poor sleep quality has a bi-directional association with medication adherence, which ultimately leads to greater HIV symptom severity, in large part due to self-reported sleep quality. It is important for future work to examine these associations prospectively as such posited bi-directional, prospective relations can only be identified in longitudinal investigations.

So as to further our understanding of the nature of these relations, we examined self-reported memory functioning as a proposed mediator of the relations described above. Contrary to prediction, self-reported memory functioning did not moderate the relation between self-reported sleep quality and HIV medication adherence. However, a significant interaction between self-reported memory functioning and sleep quality on self-reported HIV symptom severity was observed, with this interaction remaining within the context of the mediational model. Indeed, we observed that for individuals with poor self-reported memory functioning, self-reported sleep quality was not differentially associated with HIV symptom severity. Instead, self-reported sleep quality was associated with HIV symptom severity only among those with relatively good self-reported memory functioning. This pattern of findings was unexpected based on previous research showing that HIV symptom burden is higher among individuals endorsing cognitive struggles and poor self-reported memory functioning.[24,25] Findings suggest that individuals with poor memory functioning already experience so much memory impairment that the addition of poor sleep quality does not incrementally add predictive power.

Interpretation of the findings should be considered within the context of a number of limitations. First, and most importantly, this is a cross-sectional study and therefore conclusions regarding causality or temporal direction cannot be determined from the present findings. While our interpretation is strengthened by the subsidiary analyses, future research would benefit from prospective longitudinal designs in order to determine causal conclusions. Second, while we included a behavioral index of medication adherence (i.e., pill count), future research would benefit by including a multimodal assessment of adherence, as pill count can be influenced by a myriad of patient factors (e.g., dumping pills). In addition, sleep, memory, and HIV symptom severity were all assessed using self-report measures. While we sought to balance this by only including well-validated self-report measures, future research would benefit from also including objective assessments of sleep (i.e., polysomnography), memory (i.e., neuropsychological test battery), and HIV symptom severity (i.e., viral load). In addition, our self-report assessment of sleep was comprised of a single question. More detailed self-reported sleep assessments, supplemented by objective measures, would benefit future research. Third, individuals who comprised the current sample were predominately male and from the San Francisco Bay area. Future research would benefit from extending this work to samples with more women and/or from different geographic areas (i.e., rural locations). Finally, we may have been slightly underpowered for the current analyses, as a sample size of 150 would be ideal for the analyses we conducted. Future research would benefit from inclusion of larger sample sizes.

Limitations notwithstanding, the current study demonstrated that poor self-reported sleep quality is associated with both HIV medication adherence and self-reported HIV symptom severity, and partially accounts for the relation between HIV medication adherence and self-reported HIV symptom severity. In addition, self-reported memory functioning moderated the relation between self-reported sleep quality and HIV symptom severity, such that for individuals with relatively good to average self-reported memory, self-reported sleep quality had a stronger association with HIV symptom severity. Pending replication and extension of the current study, these results may offer initial clinical implications. Most notably, results suggest that among HIV positive individuals with good to average self-reported memory functioning (score below 88 on the EMQ), sleep quality should be targeted as a means of improving overall severity of self-reported HIV symptoms, particularly among those with poor medication adherence. Among individuals with poor self-reported memory functioning, these results would suggest that targeting sleep may be less beneficial and that instead, identifying ways to address and improve memory functioning (e.g., external cueing systems, clinical reminders, computerized cognitive remediation programs) may be an important target in order to improve self-reported HIV symptom severity. Overall, this study highlights the importance of including sleep and memory assessments in treatment for HIV positive individuals as a means of identifying treatment targets for those with poor medication adherence and those who are experiencing elevated HIV symptom severity.

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Address correspondence to:
Dr. Kimberly Babson
Center for Innovation to Implementation
VA Palo Alto Health Care System
795 Willow Road (152-MPD)
Menlo Park, CA 94025

E-mail: Kimberly.Babson@va.gov