Physical Symptoms, Beliefs About Medications, Negative Mood, and Long-Term HIV Medication Adherence

Jeffrey S. Gonzalez, Ph.D.
Harvard Medical School/Massachusetts General Hospital

Frank J. Penedo, Ph.D. and Maria M. Llabre, Ph.D.
University of Miami

Ron E. Durán, Ph.D.
Alliant International University

Michael H. Antoni, Ph.D. and Neil Schneiderman, Ph.D.
University of Miami

Rob Horne, MSc, MRPharmS, Ph.D.
The School of Pharmacy, University of London

ABSTRACT

Background: *Near-perfect levels of HIV medication adherence are necessary for treatment to be successful. However, many patients continue to report nonadherence to HIV treatment.* ***Purpose:*** *This study examines the relationship between symptoms of HIV and medication adherence and evaluates beliefs about HIV medications and negative mood states as potential mediators of this relationship.* ***Methods:*** *These relationships were tested with structural equation modeling using a 15-month longitudinal design. The ethnically diverse convenience sample included 325 HIV-infected men who have sex with men and women prescribed Highly Active Antiretroviral Therapy (HAART).* ***Results:*** *Results showed that a greater number of symptoms were associated with poorer medication adherence, and this relationship was partially mediated by increases in concerns about HAART. Contrary to expectations, negative mood states were not directly related to medication adherence. In the final model, concerns about HAART and general distrust of medications each predicted poorer HAART adherence. Necessity beliefs about HAART and level of educational attainment each predicted better adherence. The final model accounted for approximately 24% of the variance in HAART adherence.* ***Conclusions:*** *The results of this study suggest that Horne's (1) necessity-concerns framework can be successfully applied to identify beliefs about medication that are important predictors of adherence to HAART over time. These findings have relevance for developing interventions to improve medication adherence among HIV-infected patients.*

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INTRODUCTION

Research on individuals at risk for HIV infection and patients infected with the virus suggests that the experience of symptoms often plays a major role in various health behaviors including testing for HIV infection (2–4), seeking medical treatment (5,6), and initiation/refusal of Highly Active Antiretroviral Therapy (HAART) (7). This is consistent with the commonsense model of illness (CSM), which proposes that the experience of symptoms motivates patients to search for a cause, diagnosis, and treatment (8–10). This model posits that in the absence of symptoms individuals generally assume that they are healthy (8,10). From this perspective, HIV represents a challenge to patients' commonsense models of illness, because its treatment is frequently beset by adverse secondary effects of medication and is often initiated when patients are symptom free (1,11–13).

Although symptoms may motivate patients to seek a diagnosis and treatment for HIV, the presence of symptoms after the initiation of treatment is consistently associated with treatment nonadherence. The experience of intolerable side effects is often a primary reason given for discontinuing medication treatment (14) and reports of fewer symptoms are associated with better adherence to treatment across a variety of measures of adherence among HIV-infected men and women (15–17). Several studies of a multicenter cohort of French patients prescribed HAART have also suggested that reports of side effects and other symptoms are associated with poorer medication nonadherence over time (18–20).

These findings suggest that patients who experience symptoms while on HAART are likely to interpret their symptoms as signs that their medications are either causing them harm (i.e., causing side effects) or failing to provide symptom relief (i.e., are not effective). The study presented here sought to model the process by which symptoms are related to poorer HAART adherence by examining beliefs about medications and negative mood states as potential mediators of this relationship.

Research by Rob Horne and colleagues on the relationship of beliefs about medication to adherence has

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Reprint Address: J. S. Gonzalez, Ph.D., Department of Psychiatry, Massachusetts General Hospital, 15 Parkman Street, ACC 812, Boston, MA 02114. E-mail: jsgonzalez@partners.org

shown that reported adherence is positively correlated with *necessity* beliefs and negatively correlated with *concerns* about medication (21–23). Multivariate analyses using data from diverse illness groups (asthma, cancer, cardiac, and renal) have shown that medication beliefs are stronger predictors of reported adherence than clinical or demographic variables (21). Preliminary reports suggest that necessity beliefs are stronger among patients who attribute symptoms to HIV disease. Conversely, stronger concerns about HAART are associated with perceptions of greater personal sensitivity to adverse effects of treatment (24). Thus, symptom attributions may affect patient perception of both necessity and concern over HAART medications, which in turn could influence medication adherence.

In addition to being associated with beliefs about treatment, symptom experiences are also associated with changes in mood. Pre-HAART cross-sectional studies consistently demonstrated a positive relationship between physical symptomatology and depression among individuals (usually gay or bisexual men) living with HIV (e.g., 25–27). Longitudinal data (28) showed that physical symptom intensity was correlated with changes in depression over time in a sample of men and women with AIDS. Increases in physical symptomatology over time predicted changes in depression from baseline to follow-up in a sample of gay men with AIDS (29), and a more recent longitudinal study of gay men also showed that symptom reports were predictive of both depression and stress (30).

There is a strong body of evidence supporting the association of negative mood, especially depression, and nonadherence, both in chronic illness populations in general (for a review, see 31) and among HIV-infected patients on HAART (e.g., 32–34). However, not all studies have found significant relationships between depression and HAART adherence (e.g., 19,35,36). These somewhat inconsistent findings may be attributed to differences in samples, the measurement of depression, and/or failure to consider the role of symptoms and beliefs about medication. Although less frequently evaluated, symptoms of anxiety have also been related to poorer medication adherence among patients taking HAART (15).

Figure 1 presents the theoretical model that integrates the findings just reviewed. It draws from Leventhal's (37) parallel-processing model drawn from work in fear communications and Horne's model of treatment representations (38) and proposes that there are independent affective and cognitive determinants of health behavior. Our study investigates beliefs about HAART medications and negative mood states as potential mediators of the relationship between HIV symptom reports and HAART adherence. Higher levels of symptoms of HIV were expected to predict more negative mood states, more concerns about HAART, and less perceived necessity of HAART. Necessity beliefs were expected to predict better levels of adherence, whereas concerns about HAART were expected to be predictive of poorer adherence. More negative mood states were expected to predict poorer adherence. The relationships between HAART medication beliefs and adherence were expected to be independent of general beliefs about medicine and negative mood states.

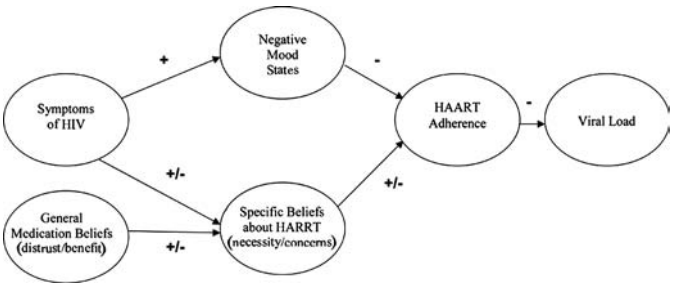

FIGURE 1 Theoretical model.

METHOD

Participants and Procedure

Participants were 325 HIV-infected men and women enrolled in a longitudinal randomized trial between 1998 and 2004 investigating the effects of a 10-week, group-based, cognitive behavioral stress management (CBSM) intervention on various outcomes in persons living with HIV. The CBSM condition was compared to a control condition where participants received one group-based informational session and were given the complete participant manual used in the CBSM intervention to read on their own. Informed consent was obtained from all participants prior to enrollment in the study. The analyses reported next include data from both control and experimental participants and do not focus on experimental effects. Experimental outcomes have been reported elsewhere for a subset of the current sample (39,40).

Participants between the ages of 18 and 65 who were currently prescribed HAART were eligible for inclusion. Excluded were participants who were prescribed medications with immunomodulatory effects, had a history of chemotherapy, had whole body irradiation, or had a history of chronic illness associated with persistent generalized lymphadenopathy or permanent immune system changes. Additional exclusionary criteria included inability to read at a sixth-grade level, significant cognitive impairment, current psychosis, drug or alcohol dependence or panic disorder, and active suicidality. Temporary exclusion criteria related to HAART regimen changes, intravenous drug use, antibiotic use, and hospitalization. Additional details of the study procedure can be found elsewhere (41,42).

Measurement of Study Variables Over Time

Participants were assessed at baseline (T1), at the completion of the intervention (T2: approximately 3 months

after initial assessment), and every 6 months for another year (T3 and T4). To maximize the reliability of our measurements, longitudinal data were used whenever possible. A series of growth curve models were tested to evaluate whether there was significant change over time, the Adherence to Combination Therapy Guide (ACTG), Medication Event Monitoring System (MEMS), and viral load data. Intercepts and slopes were estimated and the intervention's effect on each slope was also evaluated. Each variable was evaluated in two growth models: one estimated in the entire sample, and the other using group assignment as a between-subjects predictor of slope. These analyses revealed no significant slopes (change) over time for any variable and no intervention effect on ACTG, MEMS, or viral load over time, consistent with results reported by Llabre et al. (42). Thus, these variables were considered stable over time, and measurement models made use of data from all available time points to maximize reliability. Given the stability in adherence and viral load data over time, our analysis did not focus on modeling change in predictor variables. Because the intervention was likely to influence negative mood states, we used only baseline data to model the latent variable for negative mood. Baseline data were also used to measure HIV symptom reports. For beliefs about medications, growth curve modeling revealed a lack of significant change over time in subscales of the Beliefs about Medicines Questionnaire (BMQ) and a lack of a significant intervention effect on these variables. In addition, confirmatory factor analysis (reported next) demonstrated invariance of factor loadings across time points, thus establishing stability of these data over time based on stringent criteria. Therefore, beliefs about medications were modeled using mean subscale scores across all available time points.

As reported by Weaver et al. (41) and Llabre et al. (42), a second-order adherence latent factor was specified combining latent factors for self-reported adherence (four assessments taken over 15 months) and MEMS measured adherence (three assessment periods over 9 months). Similarly, viral load measurements from four assessments over the 15-month period were combined to create a latent factor of viral load. This procedure minimized the impact of random and measurement errors on our estimates of these variables and resulted in a maximized relationship between adherence and viral load. Adherence and viral load were stable over time and did not vary as a function of intervention group (40,41).

Measures

Symptom reports. Participants met with an M.D. who performed a comprehensive review of systems during a medical evaluation. This review included gastrointestinal; respiratory; genitourinary; neurological; extremities; cardiovascular; ear, nose, and throat; dermatological; metabolic; and general symptoms. Patients reported whether they had experienced any of the listed symptoms in the previous 5 weeks. Total number of reported symptoms was used in all analyses because it is difficult to objectively determine whether reported symptoms are medication side effects and the study did not asses participants' causal attributions for reported symptoms.

Beliefs about medications. The BMQ (21) was used to assess perceptions about HAART and medications in general. Participants respond to each of 31 items on a 5-point agreement scale. The general items produce two subscales: *Overuse* (3 items), the perception that providers overprescribe medicines; and *Harm* (5 items), the perception that medicines are mostly harmful. Recently, this subscale has been reanalyzed and shown to provide an additional, 4-item *Benefit* scale assessing the perception that medicines are generally beneficial (R. Horne, personal communication, January 2005). The 19 items specific to HAART produce two subscales: *Concerns* (11 items), assessing worries about the harmful effects of HAART; and *Necessity* (8 items), assessing the perceived importance of taking HAART.

For our study, confirmatory factor analysis (CFA) was performed on an updated version of the scale provided by its authors to ensure the best psychometric properties for this diverse sample as well as to allow the use of time invariant subscale means over time. Data from the three time points where the BMQ was administered were used to increase the stability of the factors. A CFA model specifying equal loadings for each item on its respective factor across time assessed the invariance of factor loadings.

The initial CFA based on published scoring protocols for the general medications scale and the HAART specific scale each showed poor fit. Several adjustments were made to each scale to limit the number of items and to minimize cross-loadings of items on more than one subscale. For the general scale, we collapsed the highly correlated Harm and Overuse subscales into a "Distrust" scale and removed a number of items (four from the Distrust subscale and two from the Benefit subscale). This two-factor model showed good fit, $\chi^2(110) = 123.71$, $p = .18$ (CFI = .98, RMSEA = 0.021 [90% CI = 0.000–0.039]). For the HAART specific scale, after the removal of items with low factor-loadings or cross-loadings (seven from the Consequences subscale and four from the Necessity subscale), the model showed good fit, $\chi^2(214) = 246.36$, $p = .06$ (comparative fit index [CFI] = .98, root mean square error of approximation [RMSEA] = 0.023 [90% confidence interval (CI) = 0.000–0.036]). The chi-square for the item-loading invariance CFA models did not differ significantly from these models (general scale $\chi^2_{\text{difference}}[8] = 5.07$; HAART specific scale $\chi^2_{\text{difference}}[12] = 19.90$) suggesting that there were no significant differences in the loadings of each item on its respective subscale across the three time points. Thus, subscale score means were computed across

the three time points for the analyses presented next. Table 1 presents the CFA results for the revised 14-item BMQ scales.

Negative mood states. Among male participants, the Profile of Mood States (43), a 65-item, 5-point adjective rating scale, was used to assess negative mood states over the previous 7 days at baseline. Only the Anger/Hostility, Depression/Dejection, and Tension/Anxiety subscales were used in our study. Because female participants completed a brief, 18-item version of the Profile of Mood States developed for this study, subscale means were used for all analyses.

Medication adherence. Two methods were used to assess HAART adherence: self-report and electronic monitoring. The ACTG (44) was used to assess the number of antiretroviral doses for a participant's drug regimen and the number of pills the participant reported skipping over the past 4 days. Adherence was calculated as number of pills taken divided by number of pills prescribed over the previous 4 days. A MEMS cap containing a pressure-activated microprocessor, which records the date and time of each opening, was provided to each participant to monitor one drug in their HAART regimen, usually the protease inhibitor. MEMS cap data were electronically downloaded using the software MEMS View (version 2.61; Aprex Corporation). Percent adherence was defined as total doses taken divided by the total doses prescribed multiplied by 100 for three periods: (a) between the first (T1) and second (T2) assessment points (approximately 90 days), (b) between T2 and 90 days afterward (T2.5), and (c) between T2.5 and the first follow-up assessment (T3 − approximately 90 days after T2.5).

TABLE 1
Beliefs about Medicines Questionnaire Confirmatory Factor Analyses Results

	Standardized Factor Loading			*Unstandardized Factor Loading*			*SE*			*Z*		
Items	*T1*	*T2*	*T3*	*T1*	*T2*	*T3*	*T1*	*T2*	*T3*	*T1*	*T2*	*T3*
General Distrust Factors												
1. Doctors use too many meds.	.49	.61	.67	.57	.69	.80	.09	.08	.09	6.72	8.40	8.79
5. Natural remedies are safer than medicines.	.49	.47	.48	.46	.44	.42	.07	.07	.07	6.76	6.30	6.01
11. Doctors place too much trust on medicines.	.67	.64	.66	.71	.69	.71	.08	.08	.09	9.20	8.65	7.99
12. If doctors had more time with patients they would prescribe fewer medicines.	.59	.55	.59	.64	.58	.59	.08	.08	.08	8.06	7.36	7.29
General Benefit Factor												
3. Medicines help many people to live better lives.	.65	.57	.51	.51	.51	.42	.07	.10	.09	7.41	5.04	4.92
10. Medicines help many people to live longer.	.59	.80	.50	.54	.74	.44	.08	.13	.09	7.07	5.56	4.83
HAART Concerns Factor												
14. Having to take these medications worries me.	.53	.67	.72	.62	.80	.82	.08	.09	.09	7.33	9.14	8.92
21. I sometimes worry about becoming too dependent on these medications.	.63	.58	.55	.73	.69	.63	.08	.08	.09	8.82	8.51	6.91
23. These medicines give me unpleasant side effects.	.54	.54	.53	.67	.68	.66	.08	.08	.09	7.91	8.10	7.21
31. The taste of this medication makes me feel unwell.	.49	.64	.46	.55	.67	.26	.08	.08	.09	6.71	8.50	2.81
HAART Necessity Factor												
13. My health, at present, depends on these medicines.	.68	.72	.68	.61	.68	.60	.05	.06	.06	11.20	11.95	9.76
19. My health in the future will depend on these medicines.	.80	.90	.67	.75	.83	.67	.06	.05	.07	13.69	16.62	9.39
26. These medicines are my best hope for the future.	.73	.81	.83	.64	.76	.70	.05	.06	.05	12.48	13.90	13.12
30. These medicines keep me alive.	.72	.83	.77	.68	.79	.72	.06	.05	.06	12.37	14.81	11.66

Note. HAART = Highly Active Antiretroviral Therapy.

Viral load. At all assessment appointments, venous blood samples were collected from participants using glass tubes containing sodium heparin (Vacutainer, Cat. #6489, Becton-Dickinson, Rutherford, NJ). HIV viral load was calculated with an AMPLICOR assay using reverse transcriptase polymerase chain reaction (U.S. #83088, Roche Laboratories, Pleasonton, CA) to measure the number of HIV virions per microliter of peripheral blood plasma. An ultrasensitive assay with a lower limit of sensitivity of 50 copies/μl was used for this study.

Modeling

A full information maximum likelihood approach that yields unbiased estimates of parameters under the assumption of missing at random (45) was used in Mplus (version 2.14; [46]). The proportion of complete data present for psychosocial variables ranged from approximately .84 to .96. For ACTG, the proportion of complete data ranged from .57 to .93. The proportion of complete data for MEMS data across time points ranged from .44 to .60. The proportion coverage for viral load ranged from .33 to .95. Although there was significant attrition over the course of the study, we believe that the assumption of missing at random can be applied to our missing data. According to state of the art recommendations (44), full information maximum likelihood approaches result in less bias than listwise deletion approaches. Prior to modeling, we examined the distribution of all variables. Viral load and ACTG measures were natural log transformed due to violations of normality. MEMS values were divided by 100 to create a metric similar to the viral load and ACTG values.

RESULTS

Sociodemographic characteristics of the sample of 325 men and women are reported in Table 2. Means, standard deviations, and internal consistency reliability of all psychosocial, adherence, and biological measures were calculated in the sample and are reported in Table 3. The table also presents the percentage of participants at each time point with greater than 90% adherence as assessed by the ACTG and MEMS and an undetectable viral load (<200 copies/ml).

Analysis

The structural equation modeling analyses were conducted in three general steps. The model was evaluated at each step, and when necessary, modifications were made to improve fit. In the first step, total symptom reports and the covariates of age, education, and pill burden were specified to predict adherence. The second step involved the inclusion of negative mood as a mediator of the relation between symptoms and adherence. The third step involved the addition of medication beliefs as a second mediator of the symptom-adherence relationship.

TABLE 2
Sociodemographic Information for Sample

Items	*Total*[a]
Gender (male)	60%
Age (years)	40.9 ± 8.5
Months since HIV diagnosis	92.2 ± 57.6
Number of HIV pills per day at baseline	2.3 ± 1.3
Ethnicity	
African American	59.9%
Non-Hispanic White	22.5%
Hispanic	12.9%
Other	4.7%
Education	
Did not graduate high school	25.5%
High school graduate or equivalent	27.3%
Some college	24.2%
College graduate	16.0%
Some graduate or graduate degree	7.0%
Employment history	
Student	12.4%
Clerical	10.9%
Semi-professional	1.9%
Professional	22.9%
Manual labor	51.9%
Currently working	24.7%
Yearly income	
Less than $10,000	64.1%
$10,001–$20,000	20.8%
$20,001–$30,000	6.1%
$30,001–$40,000	3.5%
$40,001–$50,000	2.2%
More than $50,000	3.2%

[a] $n = 325$.

Hypothesized Model

Age, time since diagnosis of HIV, education level, income, and pill burden (mean number of HIV medication doses prescribed in a 4-day window over the study period) were each evaluated as potential covariates to be included in the final model, predicting adherence. Only age (.17), education (.23), and pill burden (−.17) were retained as covariates because of significant path coefficients with the second order latent factor of adherence. First, total symptom reports were added to the covariates model to evaluate the significance of the relationship between symptoms and adherence. This model fit the data well, $\chi^2(80) = 101.15$, $p > .05$ (CFI = .97, RMSEA = .029 [90% CI = 0.012–0.048], standardized root mean square residual [SRMR] = .060) and the path (−.22) between symptoms and adherence was significant, indicating a significant direct effect of symptoms on poorer adherence. The latent variable for negative mood states was next added to the model to evaluate the relationship between negative mood and adherence and the hypothesized mediational path between symptoms, negative mood, and adherence. This model showed somewhat less than adequate fit with a significant chi-square, $\chi^2(123) = 161.39$, $p = .01$ (CFI = .971,

TABLE 3
Descriptive Statistics for Model Variables

Indicators and Factors	*Range*	*M*	*SD*	*Alpha Reliability or %*
BMQ General Benefit	1–5	4.31	.60	.57
BMQ General Distrust	1–5	2.97	.65	.80
BMQ HAART Concerns	1–5	2.71	.75	.81
BMQ HAART Necessity	1–5	4.11	.68	.78
Total reported symptoms	0–53	11.86	8.75	.91
Negative mood				
Anger/hostility	0–4	.88	.83	Women = .76 Men = .89
Depression/dejection	0–4	.82	.85	Women = .83 Men = .93
Tension/anxiety	0–4	1.22	.81	Women = .70 Men = .81
ACTG (% doses taken)[a]				
Time 1	0–100	92.25	17.48	76.9%
Time 2	0–100	92.07	20.39	79.9%
Time 3	0–100	93.3	18.07	79.4%
Time 4	0–100	92.82	21.35	80.6%
MEMS (% doses taken)[a]				
Time 1 − Time 2	0–100	58.40	33.80	26.5%
Time 2 + 90 days	0–100	59.13	39.27	37.2%
Time 2 + 90 − Time 3	0–100	49.05	41.67	32.6%
Viral load (copies/μl)[b]				
Time 1	0–700,986	16,273.23	57,928.82	51.4%
Time 2	0–294,481	14,355.02	38,709.28	54.9%
Time 3	0–190,708	13,283.92	33,573.91	57.9%
Time 4	0–623,970	20,462.57	70,339.26	50.5%

Note. BMQ = Beliefs about Medicines Questionnaire; HAART = Highly Active Antiretroviral Therapy.
[a] Percentage values represent percentage greater than 90%.
[b] Percentage values represent percentage less than 200 copies.

RMSEA = .031 [90% CI = 0.015–0.051], SRMR = .066). Contrary to expectations, although symptoms were significantly related to negative mood (.28), negative mood states were not directly associated with adherence. Beliefs about medication were next added to the model. Several modifications were made based on the results of the model. First, pill burden was no longer significantly related with adherence in this model, but based on a significant correlation with HAART concerns ($r = .22$), it was retained in the final model as a predictor of higher levels of concerns. Age was no longer significantly associated with adherence and was removed from the analysis. The addition of a direct path from general distrust of medications beliefs also significantly improved model fit. Finally, two correlated errors were added between the ACTG latent factor and symptom totals and negative mood states, suggesting a source of shared variance outside of the model possibly stemming from shared method variance. Each of these modifications improved model fit significantly based on a significant reduction in chi-square, with the final model showing good fit, $\chi^2(179) = 198.08$, $p = .16$ (CFI = 0.99, RMSEA = 0.018 [90% CI = 0.000–0.031], SRMR = 0.056; see Figure 2).

As can be seen from Figure 2, HAART concerns and necessity beliefs were each related in the expected directions to medication adherence, although the relationship was stronger for concerns than necessity. HAART specific concerns were influenced by higher general distrust beliefs and lower general benefit beliefs about medications. It is interesting to note that higher levels of pill burden also predicted higher levels of concerns such that those patients taking more pills of HAART during the study period also had more concerns about the negative consequences of HAART. Specific necessity was only significantly predicted by general benefit beliefs. Unexpectedly, general medication distrust beliefs were also directly associated with medication adherence. This negative relationship is independent of the hypothesized indirect relationship to adherence through increased specific concerns. The hypothesized indirect effect for general distrust on adherence through specific concerns was also significant ($z = 2.33$, $p = .02$), suggesting that higher general distrust beliefs predict poorer adherence through both indirect and direct pathways. Symptom reports also showed a significant indirect path to adherence through associated elevations in HAART

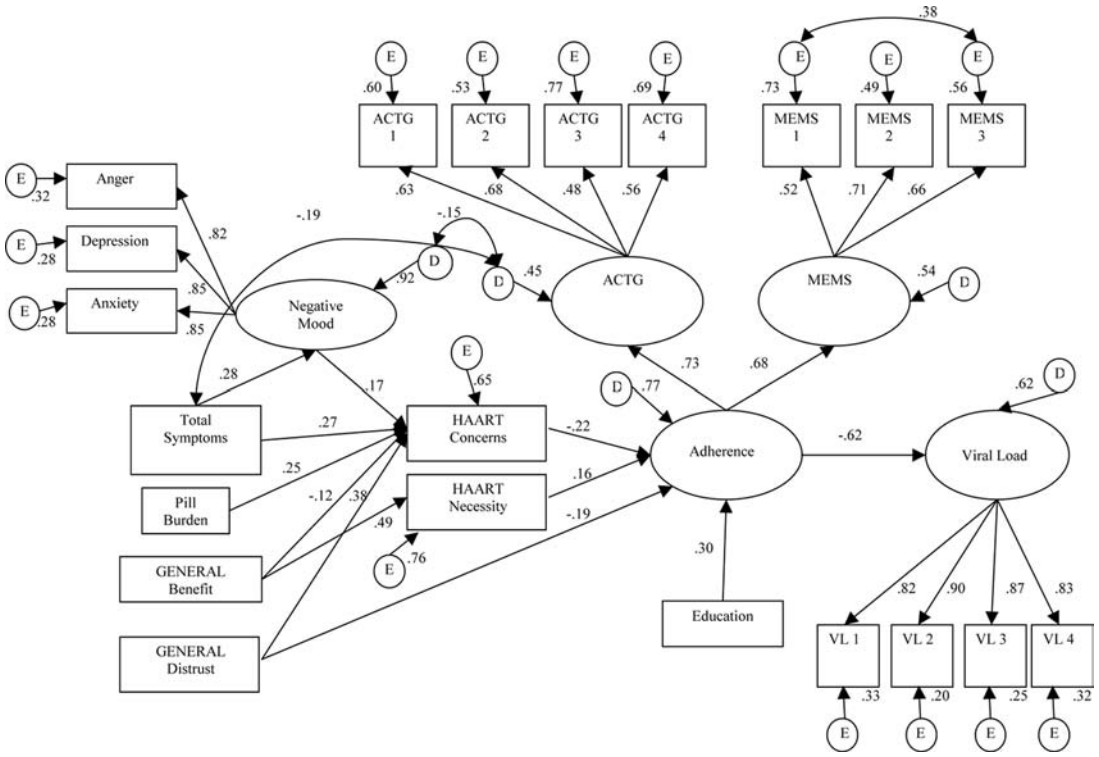

FIGURE 2 Standardized parameter estimates of the final model. *Note*. Large ovals represent latent factors; rectangles represent indicators of each latent factor; small circles labeled E represent residual variance associated with each indicator; and small circles labeled D represent residual variance in the latent factors. All paths and factor loadings are significant ($p < .05$). R^2 for the latent variables were .55 for Adherence to Combination Therapy Guide, .46 for Medication Event Monitoring System, .38 for viral load, and .24 for adherence. Model fit statistics: $\chi^2(179) = 198.08$, $p = .16$ (CFI = 0.99, RMSEA = 0.018 [90% CI = 0.000–0.031], SRMR = 0.056).

concerns ($z = 2.16$, $p = .03$). The indirect effect of negative mood states on adherence through elevations in HAART concerns fell short of significance ($z = 1.90$, $p = .06$). The final model accounted for approximately 24% of the variance in second-order latent factor adherence scores and approximately 38% of the variance in viral load.

DISCUSSION

This study builds on previous work that seeks to understand treatment adherence from the patient's perspective using the CSM of self-regulation as a theoretical guide (10). The CSM and extensions to this model incorporating treatment perceptions (1,38) were utilized to guide the development of a theoretical model (Figure 1) relating these factors (i.e., symptom reports, medication beliefs, negative mood states, and HAART adherence). Leventhal's parallel processing model (37) suggested separate cognitive and emotional mediational pathways between symptoms of illness and adherence. Within this theoretical framework, our study evaluated the relationships of symptoms of HIV, beliefs about medications in general, beliefs about HAART medications, and negative mood states to HAART adherence in a diverse sample of HIV+ men and women. Although previous research has shown that medication beliefs are related to better adherence to treatment recommendations in a variety of illness groups (1), this is the first study utilizing the BMQ in the United States with ethnically and socioeconomically diverse HIV+ male and female patients. To maximize the accuracy of our measure of adherence, we employed a structural equation modeling approach that makes use of multiple measurement methods and multiple time points of measurement to minimize the impact of measurement error on estimates of HAART adherence (41,42).

The hypothesized model was partially supported by the data: higher numbers of symptoms significantly predicted worse adherence over time, and this relationship was partially mediated by higher levels of HAART concerns. Contradicting the hypothesized model, symptoms were not related to adherence through negative mood states. Symptoms were related to neither HAART necessity beliefs nor general distrust or benefit beliefs. Each of the medication beliefs that were related to adherence (general distrust, HAART concerns, HAART necessity) remained significant predictors of adherence after ruling out the potential confound of negative mood. Thus, the cognitive pathway depicted in Figure 1 is largely independent of negative mood states and, at least in this sample, is more

important in predicting HAART adherence over time than the emotional pathway. Negative mood did predict increased HAART concerns, but it was not related to other medication beliefs.

The positive relationship between symptoms and HAART concerns is consistent with expectations based on the CSM and Horne's extended self-regulatory model (1). This could reflect that patients were interpreting their symptom experiences as side effects of HAART. However, it is difficult to differentiate between symptoms associated with HIV progression and side effects of HAART using any objective criteria. Thus, it would be important to rely on the patient's evaluation of whether a symptom is a sign of illness or a side effect in differentiating between symptom groups (e.g., 11). The relationship between symptoms of HIV, side effect symptoms, and adherence deserves further investigation.

The lack of a direct relationship between negative mood states and adherence in our study is inconsistent with previous reports that have found such a relationship (e.g., 32–34). However, there have also been a number of null relationships reported between negative mood states or depression and adherence to HIV medications (e.g., 19,35,36). This inconsistency could represent inconsistency in the measurement of mood across these studies. For example, in our study we measured negative mood states, not the presence of clinically significant mood disorder. The results of our study, however, suggest another possibility. The significant path correlating the error variance of the negative mood and ACTG latent factors, along with the lack of a relationship between the negative mood and adherence factors, suggest that previously reported relationships between negative mood states and adherence could, in part, reflect shared method variance between self-reports of negative mood states and self-reported adherence. An additional possibility for this inconsistency could be the lack of attention given to determinants of negative mood states and a lack of attention to discriminating between negative affects. For example, fear and distress about HIV may motivate adherence, whereas distress about medication side effects could lower adherence. It is also possible that these relationships vary as a function of disease severity. For example, we have reported that CBSM-associated decreases in viral load, among a subset of men who have sex with men with detectable viral loads, were mediated by decreased depressed mood (39). This issue deserves further investigation with more attention to disentangling disease-related, treatment-related, and general negative mood states as predictors of adherence behavior.

This study identified several factors that predict concerns about HAART. In addition to being positively predicted by higher levels of symptoms and negative mood states, concerns were also positively predicted by pill burden and distrust of medications in general. HAART concerns were negatively predicted by perceptions of benefit of medications in general. The direct and indirect (through elevations in HAART concerns) effects of general distrust beliefs on HAART adherence suggest that these beliefs are particularly important in the prediction of adherence to HAART and should be evaluated carefully. Necessity beliefs were less related to factors measured in our study. Only general benefit beliefs predicted HAART necessity beliefs. These results indicate that interventions aimed at changing medication beliefs could be successful in improving adherence outcomes among similar HIV+ populations. The findings also begin to provide empirical information about the possible determinants of these beliefs. Further research is needed to more fully understand factors that influence these beliefs and how they can be modified through intervention.

It is important to recognize the role of education level in the results of our study. Level of education was positively associated with HAART adherence in the final model even after controlling for beliefs about medications and other predictors. Thus, the variables in our model could not explain this relationship. Medication beliefs also appear to be independent of educational attainment.

Several limitations to our study should be noted. First, data from intervention and control participants were combined for all analyses. This presented some limitations on our ability to model variables over time. We used only baseline data to model the latent variable for negative mood and to measure HIV symptom reports. Growth curve modeling showed no evidence of significant change over time or significant intervention effects on variables for which we did use longitudinal data (i.e., ACTG, MEMS, viral load, and beliefs about medication). Although other reports from our group have reported on intervention effects (39,40), these effects were found in predefined subsets of this sample and did not involve any variables in our model except for viral load (39). The viral load finding was only significant for a subset of 101 men who have sex with men with detectable viral loads at baseline and was not mediated by any variables in our model. Thus, we feel confident that though we collapsed data from control and intervention participants for our analyses, we were successful in ruling out the possibility of intervention effects on the variables in our model. Further longitudinal and intervention-based investigations are needed to validate the causal pathways we propose in our model. Second, although our sample was quite diverse including a substantial number of women, heterosexual men, and members of ethnic minority groups, use of a convenience sample of paid participants who were recruited for an intervention study may limit the generalizability of the results to other groups of people living with HIV. In addition, our inclusion and exclusion criteria may further influence the representativeness of our sample. Generalizing these results to the wider population of patients infected with HIV may not be warranted. Third, it is important to emphasize that our measurement of negative mood focused on mood states and not clinical diagnoses of mood or anxiety disorders.

Therefore, it is not possible to ascertain how our results might have differed if diagnosis was used as a criterion for evaluating mood disruption rather than mood state. Fourth, our data did not demonstrate significant systematic change over time. Although the stability of these data allowed us to maximize our use of multiple data points, thus improving the precision of our measurements, we were unable to model how changes in predictors may influence changes in adherence over time. Finally, our study did not assess other variables that may have improved the prediction of adherence. For example, it is not known how patients' beliefs about HIV and their interpretations of their symptom experiences may have been related to HAART adherence and our prior work has suggested that social support and positive states of mind may also have important relationships to HAART adherence (33). The findings are consistent with other studies in HIV and other chronic medical conditions in demonstrating the utility of the necessity-concerns framework (38) as a method for operationalizing salient medication beliefs influencing adherence. Results also provide tentative support for the utility of embedding the necessity-concerns framework within the CSM.

There is a great need to address problematic adherence in HIV from a clinical and public health perspective. Although some interventions have been successful in improving adherence (e.g., 47–50), the mechanisms for change have yet to be identified. The results from this study may guide the development of future interventions for this population. Results suggest that it may not be sufficient to decrease negative mood states as several interventions have proposed (see 51 for a review), especially in samples that do not report high levels of distress. Interventions that target patients' beliefs about HAART and the factors that influence these beliefs may be effective. Future studies are needed to evaluate whether such interventions could be successful in improving adherence and HIV outcomes for this population.

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