

A Structural Equation Model of HIV-related Symptoms, Depressive Symptoms, and Medication Adherence

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Abstract

Adherence to combined antiretroviral therapy (cART) remains critical in management of HIV infection. This study evaluated depression as a potential mechanism by which HIV-related symptoms affect medication adherence and explored if particular clusters of HIV symptoms are susceptible to this mechanism. Baseline data from a multi-visit intervention study were analyzed among 124 persons living with HIV (PLWH). A bifactor model showed two clusters of HIV-related symptom distress: general HIV-related symptoms and gastrointestinal (GI) symptoms. Structural equation modeling showed that both general HIV-related symptoms and GI symptoms were related to higher levels of depressive symptoms, and higher levels of depressive symptoms were related to lower levels of medication adherence. Although general HIV-related symptoms and GI symptoms were not directly related to adherence, they were indirectly associated with adherence via depression. The findings highlight the importance of early recognition and evaluation of symptoms of depression, as well as the underlying physical symptoms that might cause depression, to improve medication adherence.

Keywords: Adherence; Depression; Antiretroviral; HIV; Symptoms; Gastrointestinal

Introduction

Advances in combined antiretroviral therapy (cART) in the United States have transformed HIV infection from a life-threatening fatal disease into a manageable chronic condition. Although several studies suggest that lower levels of adherence to cART may still be successful in suppressing the virus with newer drug regimens or certain drug class combinations [1-3], high levels of adherence remains as the treatment goal for persons living with HIV (PLWH) to effectively manage the disease [4] and to reduce the development of drug resistance [5]. Despite its importance, many PLWH struggle with adherence.

A considerable body of evidence shows an association between HIV symptoms and adherence [6-9], yet the mechanisms underlying the relationship between HIV-related symptoms and adherence is unclear. Common HIV-related symptoms include myalgia, fatigue, weakness, insomnia, weight loss, anorexia, fever, chills, night sweats, lipodystrophy, and swollen glands. Symptoms can be categorized by the organ system in which they occur. For example, symptoms in the gastrointestinal (GI) system include bloating, nausea, vomiting, constipation, diarrhea; symptoms in the integumentary system include rash and skin lesions; symptoms in the respiratory system include shortness of breath and cough; and symptoms in the nervous system include severe headaches, visual difficulties, dizziness, tingling, numbness, and cognitive impairments [10]. Many of these co-occur and overlap with side effects from cART regimens, complicating the isolation of their origin [11].

PLWH also experience psychological symptoms, particularly symptoms of depression [12-14], which in turn has multiple consequences that result in affective, physical, cognitive, and behavioral changes such as

suboptimal adherence to cART [12,15,16]. Depression is one of the most common comorbid conditions in PLWH with prevalence estimates as high as 37% [14]. Depression is related to negative self-evaluations and depressed individuals are more likely to have difficulty with daily activities (e.g., medication management, driving, and cognitive function) compared to their non-depressed counterparts [17]. Negative self-evaluations perpetuate the vicious cycle of depression and cumulatively interfere with adherence to cART and self-care.

Although previous studies have shown direct associations between HIV-related symptoms and adherence, the mechanisms underlying these associations are unknown. The present study sought to delineate the process by which HIV-related symptoms are related to cART adherence by examining the symptom of depression as a mediator of this relationship. The identification of potential mediators could serve as important intervention targets for improving self-management behaviors in PLWH. We hypothesized that HIV-related symptoms would be related both to depression and medication adherence and that there would be a mediating effect of depression on the relationship between HIV-related symptoms and adherence. We also sought to explore whether, if any, specific HIV symptom clusters are independently associated with depression and adherence.

Methods

Sample

Participants in this study were recruited for a multi-visit intervention study. The purpose of the multi-visit intervention study was to examine whether an electronic intervention targeting improvements in health literacy could influence better antiretroviral medication adherence. More

detailed descriptions of the intervention and study procedure can be found elsewhere [18]. Participants were recruited between May 2010 to December 2011 from HIV primary care clinics in South Florida and via self-referral through word of mouth. Inclusion criteria were: (1) Currently treated for HIV infection with an antiretroviral medication and stable on that medication for at least 30 days; (2) Able to provide informed consent based on clinician's assessment of their cognitive status; (3) 18 years of age or older; and (4) Able to communicate comfortably in English. Exclusion criteria included: (1) Psychiatric illness of sufficient severity as to interfere with participants' ability to understand key elements of the informed consent process or to affect their ability to participate in the intervention (e.g., active schizophrenic disorder that was not adequately treated); (2) History of head trauma with significant loss of consciousness; (3) Other neurological disorder that would interfere with a participants' ability to give informed consent or participate in the intervention (e.g., active CNS infection). The baseline data from the 124 participants in the parent study are included in the current analysis.

Measures

Automated computer-administered self-interview (ACASI; Bethesda, MD: Questionnaire Development System) was used to obtain all of the self-report data including the demographics, HIV-related Symptoms, and Depression.

Demographic data: Participants' age, ethnicity, education level, annual income, and employment status were assessed through a demographic questionnaire.

HIV-related medical information: HIV disease-related medical information including the mode of infection, duration of HIV disease and length of time on antiretroviral treatment were obtained from participants' self-report. Most recent (within 3 months of study entry) CD4+ T cell counts and viral loads were drawn from participants' clinical laboratory reports.

HIV-related symptoms: The 20-item, self-reported HIV Symptom Index [19] used in the AIDS Clinical Trial Group (ACTG) Baseline Adherence Questionnaire [20] was utilized to evaluate HIV-related symptom distress. A 5-point Likert-scale was used to indicate whether the symptom is present ("I do not have this symptom= 0) and if present, how bothersome the symptom has been (1="it doesn't bother me; 2=it bothers me a little; 3=it bothers me; and 4=it bothers me a lot) during the past 4 weeks. Symptoms were considered if they occurred during the past 4 weeks. The validity of this instrument for measuring HIV symptoms has been previously established [19]. Due to the overlap with items on the depression measure, one item related to depression in HIV Symptom Index ("felt sad, down, or depressed") was removed.

Seven items used to assess depression in the ACTG Baseline Adherence Questionnaire [20] were included as the measure of depression. These items were drawn from the Center for Epidemiological Studies depression scale (CES-D) [21]. Respondents were asked "In the past week how often did you..." 1. "Feel like you couldn't shake off the blues even with help from your family and friends?"; 2. Have trouble keeping your mind on what you were doing?"; 3. "Feel that everything you did was an effort?"; 4. Have trouble sleeping?"; 5. "Feel lonely?"; 6. "Feel sad?"; and 7. "Feel like you just couldn't 'get going?'. Items were rated on a 0–3 scale (0 = never/rarely and 3=mostly or always).

Adherence: Adherence to cART was measured using the Medication Event Monitoring System (MEMS, Aardex Group Ltd, Sion, Switzerland). This electronic device was placed on each participant's medication; it electronically records the date and time of each pill bottle opening. Adherence was calculated as the number of doses taken correctly during each 24-hour period over the 30 days following the baseline study visit

during which both HIV-related symptoms and depression data were collected.

Covariates: Variables known to be associated with medication adherence, including demographics (age, gender, race), and cognitive functioning, were included as covariates.

Cognitive function: *Crystallized general cognitive abilities* were measured using the sum of scores from the Vocabulary and Information subtests of the Wechsler Adult Intelligence Scale-IV (WAIS-IV) [22]. These subtests measure word knowledge and general information and reflect a person's acquired knowledge and communication ability. *Fluid general cognitive abilities* were measured by summing scores from the Block Design and Matrix Reasoning subtests of the WAIS-IV [22] that measure capacity to reason and solve novel problems. In addition, a measure of *long-term verbal memory* (the Logical Memory Delayed Recall Score from the Wechsler Memory Scale-IV; Wechsler [23] was included. All cognitive scores were age-adjusted.

Data analysis

Descriptive statistics and bivariate analyses were first conducted. Demographic variables significantly correlated with cART adherence ($p < .10$) were included in further analyses. Significant demographic variables, crystallized and fluid cognitive abilities and long-term verbal memory were entered as covariates.

We evaluated several approaches to isolate specific symptom clusters in the HIV symptom index [19]. Exploratory factor analyses were completed using SPSS Version 22, basing the number of factors to retain on the screen test. The model suggested by this exploratory analysis, however, was difficult to interpret as it lacked a clear interpretable structure. Further, when follow-up confirmatory analysis was completed, the model suggested by the exploratory analysis did not provide a good fit to the data. Both exploratory and confirmatory factor analyses, however, indicated that the items in the HIV symptom index primarily reflect general HIV-related symptoms. Through additional exploration of relations among items and assessment of model fit, a separate subscale comprising gastrointestinal (GI) symptoms was isolated in a bifactor model [24], similar to results reported by Holzemer [25] using a different set of HIV-related symptoms. These two components of the index (general HIV-related symptoms and GI symptoms) were used to explore the relationships among HIV-related symptoms, depression, and medication adherence in structural equation models. Confirmatory factor and structural equation analyses were completed using the MPlus statistical software version 7.2 [26], with the bifactor analysis yielding general HIV-related and GI symptom factors and the structural model estimated simultaneously. We also assessed the relative importance of general HIV-related symptoms compared to GI symptoms by evaluating their standardized coefficients.

Results

Of 124 study participants, most were men (71%) and Black/African American (61%) or white/non-Hispanic (35.5%). The mean age of participants was 47 years ($SD=8.69$). Nearly 85% of the sample had CD4+ T cell counts greater than 250 cells/mm³, and 64% had suppressed HIV viral load. Half of the sample had been living with HIV for nearly 16 years. The descriptive data of the study participants are presented in Tables 1 and 2. The most common GI symptoms reported were bloating (48%) and diarrhea (43%). In the GI symptom factor, "nausea/vomiting" and "diarrhea" items had the highest loadings.

Results of the structural model are presented in Tables 3 and 4 and graphically illustrated in the Figure 1. Both general HIV-related symptoms and GI symptom factors were related to higher levels of depressive symptoms ($p < .001$ and $p = .002$, respectively), and that higher levels of

	N	Minimum	Maximum	Mean	Std. Deviation
Age	124	20	67.00	47.10	8.69
CD4+ T cell ^a	124	62	1734.00	501.23	289.29
Viral Load ^b	124	0 ^c	2321K	23K	21K
Years Since First Treatment	123	.25	24.00	11.60	7.18
HIV Meds Doses Per Day	124	1	8.00	2.83	1.50

Table 1: Description of Sample

^aCD4+ T cell count was measured in cells/mm³

^bViral load was measured in copies/mL

^cUndetectable level

Measure ^a	N	Minimum	Maximum	Mean	SD
Crystallized Abilities	124	7	26	16.34	4.35
Fluid Abilities	124	4.00	30.00	15.48	5.79
WMS-IV Delayed	124	1	15	7.60	3.05
MEMS Correct (%)	118	6.9	100.0	81.46	20.95

Table 2: Description of Sample for Cognitive Measures and Correct Level of Adherence

SD: Standard deviation; WMS-IV: Wechsler Memory Scale, 4th ed. Logical Memory subtest, delayed recall; MEMS: Medication Event Monitoring System.

^aCrystallized Abilities: Sum of scaled scores for WAIS-IV Information and Vocabulary subtests; Fluid Abilities: Sum of scaled scores for WAIS-IV Block Design and Matrix Reasoning subtests

		Coefficient	SE	Z score	p-value	
Depression	ON					
	General symptoms	0.43	0.12	3.59	<0.001	0.000
	GI Symptoms	0.42	0.14	3.10	0.002	0.002
Adherence	ON					
	General symptoms	2.69	2.05	1.31	0.19	0.189
	GI Symptoms	1.00	2.38	0.42	0.68	0.675
	Depression	-5.12	2.10	-2.44	0.002	0.015
Adherence	ON					
	Age	0.32	0.22	1.45	0.15	0.151
	Gender	-3.94	4.67	-0.84	0.40	0.398
	Race	-5.79	4.46	-1.30	0.19	0.194
	Crystallized Abilities	-0.43	0.48	-0.90	0.37	0.369
	Fluid Abilities	0.45	0.55	0.83	0.41	0.409
	WMS Delayed Recall	0.39	0.69	0.57	0.57	0.566

Table 3: Regression Models for Structural Equation Model Paths

GI: Gastrointestinal; SE: Standard error; WMS: Wechsler Memory Scale, 4th ed. Logical Memory subtest, delayed recall

depressive symptoms were related to lower levels of medication adherence ($p=.015$). General HIV-related symptoms were not directly related to adherence ($p=.189$). The indirect effect of general HIV-related symptoms on adherence, as mediated by depression, however, was statistically significant ($p=.043$; Figure 1, curved line). This indirect effect suggests

	Estimate	S.E.	Est./S.E.	p-value
Effects from General HIV-related Symptoms to Adherence				
Total	0.495	1.87	0.264	0.791
Total indirect	-2.19	1.08	-2.025	0.043
Specific Indirect Effect				
Adherence				
Depression				
General HIV-related Symptoms	-2.19	1.08	-2.025	0.043
Direct				
Adherence				
General HIV-related Symptoms	2.69	2.048	1.313	0.189
Effects from GI Symptoms to Adherence				
Total	-1.155	2.211	0.522	0.682
Indirect	-2.154	1.086	-1.984	0.047
Specific Indirect Effect				
Adherence				
Depression				
GI Symptoms	-2.154	1.086	-1.984	0.047

Table 4: Direct and Indirect Effects of Depression

SE: Standard error; Est: Estimate

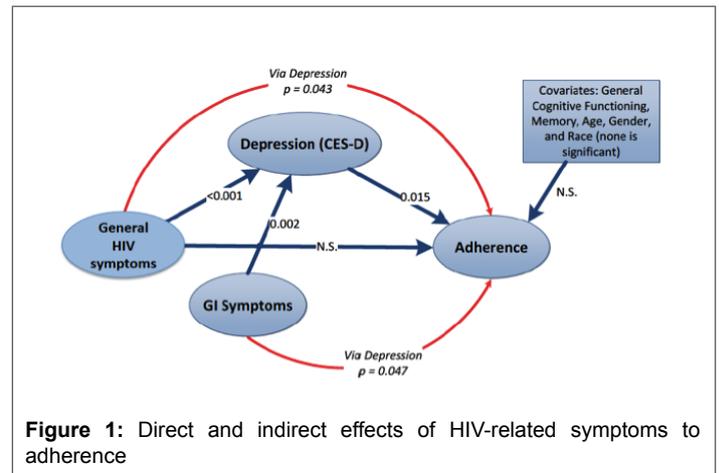


Figure 1: Direct and indirect effects of HIV-related symptoms to adherence

that higher levels of general HIV-related symptoms are related to higher levels of depressive symptoms, which are, in turn, negatively related to adherence. Additionally, the indirect effect of GI symptoms on adherence via depression was also statistically significant ($p=.047$), and the direct effect of GI symptoms on adherence was statistically non-significant ($p=.682$).

The standardized coefficients for general HIV-related symptoms and GI symptoms were similar ($.37$ [SE=.09] for general HIV-related symptoms and 0.36 [SE=.10] for GI symptoms) and the significance of the difference between the two was not statistically significant ($z=1.31$, $p=.26$). Results suggest that both groups of symptoms had a relation to depression that was similar in magnitude.

Discussion

The purpose of this study was to evaluate depression as a mediator of the relationship between HIV-related symptoms and antiretroviral

adherence, and to explore if particular clusters of HIV-related symptoms were related to depression and adherence. Although both depression and HIV-related symptoms have been related to non-adherence, only one study, to our knowledge, has evaluated the effect of HIV-related symptoms on adherence via depression [27]. Our findings suggest that the effect of general HIV-related symptoms on reduced medication adherence is explained by symptoms of depression and are inconsistent with the study by Gonzalez et al. [27]. This inconsistency may be due to the differences in measures used to assess depression. Gonzalez et al. [27] used the 65-item Profile of Mood States (POMS) for male participants and its shorter 18-item version for female participants. The POMS is not specific for symptoms of depression, but instead assesses multiple dimensions of affect through adjectives describing moods or feelings. The POMS includes six subscales of anger-hostility, tension-anxiety, depression-dejection, vigor-activity, fatigue-inertia, and confusion-bewilderment [28]. Their study analyzed three subscales of POMS, including depression-dejection, to explain the relationship between HIV-related symptoms and adherence, and found no statistically significant findings. The POMS and the ACTG depression scale used in our study utilize different approaches to measure negative mood and may account for the discrepant findings.

The relationship between HIV-related symptoms and depression in our study is consistent with previous findings in both persons living with HIV and in the general population such that patients with more physical symptoms reported more symptoms of depression [29-31]. Physical symptoms are a common manifestation of depression, particularly if the symptoms are multiple, unexplained, or persistent [29].

We also found a cluster of GI symptoms that were independently associated with symptoms of depression. These findings were similar to a recent qualitative study that reported diarrhea, one common type of GI symptom, aggravated emotional distress in older PLWH [32]. In their study, PLWH reported that the reasons for emotional distress were due to uncertainty and fear of why they were experiencing diarrhea, and shame and internalized stigma for experiencing diarrhea [32]. Studies that have included seronegative community-dwelling individuals have indicated similar findings [33,34]. Masand et al. [34] found that clinically depressed patients were more likely to meet the diagnostic criteria for irritable bowel syndrome than non-depressed patients. Similarly, Haug et al. [33] found that symptoms of depression were a significant predictor of GI symptoms including nausea, heartburn, diarrhea, and constipation.

Our results also indicated that depression mediated the association between GI symptoms and cART adherence, but there was no direct association between GI symptoms and cART adherence. This suggests the importance of assessing and treating GI symptoms to relieve depression, which might affect its downstream effect on adherence. It might be that the persistent GI symptoms reduce quality of life, thereby increasing more symptoms of depression and reducing motivation to engage in health-promoting behaviors. While persistent symptoms of GI can be stressful, it might also induce inflammation in the gut, affecting the gut-brain pathway. It is well-established in the literature that there is a bidirectional signaling between the gut and the brain, which is important in maintaining homeostasis [35]. Increasing evidence suggests that microbiota within the gut can affect brain function and behavior [36], and that the gut microbiota might contribute to anxiety and depression [35]. Studies also suggest that depression is a neuropsychiatric manifestation of gut inflammation and that treating GI symptoms could perhaps improve quality of life and reduce symptoms of depression [35]. To our knowledge, this is the first study to quantitatively examine the relation of a GI symptom cluster to depressive symptoms in HIV infected individuals, and how symptoms of depression affect the association between GI symptoms and adherence.

Given that both general HIV-related symptoms and GI symptoms are linked to depression, future research could further examine additional

mediating and potential moderating factors—such as locus-of control, uncertainty, quality of life, or stigma. Additionally, although it is difficult to determine the root cause of GI symptoms experienced among HIV-infected individuals (i.e., whether it is caused by HIV infection or medication), examining the underlying biological mechanism of symptoms of GI could offer areas for development of novel treatment strategies for both symptoms of GI and depression [35,37].

Consistent with a robust body of evidence supporting the association of depression and medication non-adherence, symptoms of depression were associated with worse adherence among participants in the current study [9,15,16]. Contradictory to our hypothesis, there was no direct effect of HIV-related symptoms on adherence. Past studies have shown that HIV-related symptoms are directly associated with poor adherence [6,7]. Our inconsistent finding may be explained by the fact that our analyses included a number of potential confounders, such as depressive symptoms, cognitive function, age, gender, and race, which may not have been included in previous studies. Further, our relatively small sample size may have reduced the power of the statistical model to detect such an association. Variability in measures of adherence and in symptoms across studies may also contribute to this finding. The current study used MEMS instead of a self-report adherence measure. Utilization of electronic monitoring devices for measuring adherence like MEMS is considered to be one of the most accurate, objective methods available [38]. Also some of the previous studies examining the association between HIV-related symptoms and adherence have used the Memorial Symptom Assessment Scale (MSAS) to assess symptom frequency and intensity. Although widely used in HIV-infected individuals, MSAS is a multidimensional scale that assesses multiple symptoms common in patients with cancer and is not necessarily specific to PLWH.

Findings from this study should be considered within its limitations. Participants were a convenience sample of volunteers from outpatient HIV treatment clinics and thus findings may not be generalizable to all PLWH. The cross-sectional nature of the study analysis prevents causal inferences about the relationships among variables that we observed. Other potentially important variables that may affect medication adherence such as health beliefs, HIV stigma, and social support were not measured in the present study and may be important to consider in future studies. Utilization of more robust measures for variables of interest could have resulted in more promising results. Specifically, our use of the ACTG depression scale may serve as one of the limitations for the study. Although seven items of the ACTG depression scale were drawn from the widely used CES-D, the relation between the ACTG depression items and the CES-D may not be comparable because the response scale for ACTG scale is different from the CES-D scale. Due to the nature of secondary data analysis, we were unable to utilize a more robust measure of depression. Limitations inherent with self-report measures may also have influenced our results. Finally, the relationship between symptoms and depression may not simply be a unidirectional association but may be a bidirectional association. It may be that general physical symptoms related to HIV infection exacerbate depressive symptoms or vice versa, creating a vicious cycle. The sample size was not sufficient to conduct a more complicated statistical model to test bidirectional relationships between our variables of interest.

Our findings show that depressive symptoms play a role in explaining the relationship between HIV-related symptoms and medication adherence, a new finding in this area, and those HIV-related symptoms and GI symptoms are independently associated with depressive symptoms. Early recognition and evaluation of symptoms of depression may, therefore, be helpful in proper management of both HIV-related symptoms and medication adherence. Interventions to reduce both HIV-related symptoms and depressive symptoms may be important to maintain

optimal cART adherence. Finally, it may be important to recognize GI symptoms in order to manage depressive symptoms and, ultimately, to improve adherence in HIV infected individuals.

Disclosures

The authors report no real or perceived vested interests that relate to this article that could be construed as a conflict of interest.

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