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The relationship between gastrointestinal symptom attribution, bothersomeness, and antiretroviral adherence among adults with HIV

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Abstract

Patients who attribute their symptoms to HIV medications, rather than disease, may be prone to switching antiretrovirals (ARVs) and experience poor retention/adherence to care. Gastrointestinal (GI) symptoms (e.g., nausea/vomiting) are often experienced as a side effect of ARVs, but little is known about the relationship of symptom attribution and bothersomeness to adherence. We hypothesized that attribution of a GI symptom to ARVs is associated with a reduction in adherence, and that this relationship is moderated by the bothersomeness of the symptom. Data for our analysis come from the pre-randomization enrollment period of a larger study testing an adherence improvement intervention. Analyses revealed that patients with diarrhea who attributed the symptom to ARVs (compared to those who did not) had significantly worse adherence. We did not find a significant moderating effect of bothersomeness on this relationship. Incorporating patient beliefs about causes of symptoms into clinical care may contribute to improved symptom and medication management, and better adherence.

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Keywords

HIV/AIDS; antiretroviral medication; adherence; MEMS; symptom attribution

Introduction

In the United States, the prevalence of HIV is estimated at more than 1 million adults and adolescents (CDC, 2016). The rate of new diagnoses has been relatively stable over the past decade, but remains high with around 40,000 people being newly diagnosed in 2015 (CDC, 2016). Through effective treatments, such as highly active antiretroviral therapy (HAART), HIV can be managed much like other chronic illnesses (e.g., diabetes) (Roberson, White, & Fogel, 2009; Weeks & Alcamo, 2010). In addition, studies have shown that the risk of HIV transmission between sero-discordant sexual partners (i.e., one partner is HIV positive and the other is not) is reduced when the HIV positive partner is on effective antiretroviral medication (Smith, Powers, Muessig, Miller & Cohen, 2012). Research has also shown that HIV incidence declines when the number of individuals on HAART increases (Montaner et al., 2010).

When HAART is not taken regularly as prescribed, an individual's HIV viral load may rise, and drug resistant strains of the virus can arise (Weeks & Alcamo, 2010). Viral resistance reduces the effectiveness of Antiretroviral Therapy (ART), making it more difficult to stop the epidemic as well as threatening public health. Therefore, maintaining adherence to antiretroviral medication regimens (ARVs) is essential for keeping individuals healthy and preventing further transmission of the virus (Baillargeon et al., 2009; Moir et al., 2010; Volkow & Montaner, 2010).

Several barriers to ARV medication adherence have been identified in the literature, such as drug use and mental health disorders (Aragónés, Sánchez, Campos, & Pérez, 2011; Keuroghlian et al., 2011; Malta, Strathdee, Magnanini, & Bastos, 2008; Mellins, Kang, Leu, Havens, & Chesney, 2003; Phillips, 2011; Swan, 2015), unstable housing or homelessness (Lanier & Paoline III, 2005; Meyer, Chen, & Springer, 2011; Nunn et al., 2010; Phillips, 2011; Rebholz, Drainoni, & Cabral, 2009; Rich et al., 2001), and experiencing side effects (Gay et al., 2011; Kremer et al., 2009; Lenzi, Wiens, & Pontarolo, 2013). Attributing symptoms to HIV medications (i.e., as side effects) is associated with switching ARVs, and poor retention/adherence to care (Batchelder, Gonzalez, & Berg, 2014; Kremer et al., 2009; Lenzi, et al., 2013). This relationship is the focus of this article.

Gastrointestinal symptoms (e.g., nausea/vomiting) are among the most common side effects of ARVs and have been shown to negatively affect adherence to medications (Johnson, Stallworth, & Neilands, 2003; Lenzi et al., 2013). However, less is known about the relationship between attributing a GI symptom to ARVs, how bothersome that symptom is, and adherence to the ARV regimen. We seek to explore these relationships in this article. Specifically, we are evaluating GI symptoms in three ways: presence of the symptom, attribution of the symptom as an ARV side effect, and bothersomeness of the symptom. Symptom attribution relationships may be important in guiding symptom and medication management.

Conceptual model

The conceptual model we used to guide our analysis was adapted from Leventhal's Common Sense Beliefs Model, as used by Scott and colleagues in their theorizing about symptom appraisal and help-seeking behaviors (Scott, Walter, Webster, Sutton, & Emery, 2013). According to this model, health-related behavior is influenced by a process of interpreting and evaluating somatic disturbances, i.e., symptoms. After experiencing a symptom, an individual assesses that symptom through cognitive and emotional responses that may be fueled by a variety of "heuristics", such as novelty of the symptom, severity of the symptom, prevalence of the symptom in one's community, and so on. These responses influence the appraisal of a symptom which then leads to coping behavior(s). The process from appraisal to coping behavior invokes if-then logic, such as "IF I believe my headache is due to dehydration, THEN I will drink water" (Scott et al., 2013, p.54).

Using this model as a framework and based on the extant literature, we developed two hypotheses: first, attribution of a GI symptom to ARV medications will reduce adherence to those medications (e.g., IF my GI symptom is due to my ARVs, THEN I will be less likely to take them) (see the arrow labeled "Hypothesis 1" in Figure 1). Second, the relationship between symptom attribution and adherence will be moderated by the bothersomeness of the symptom (see the arrow labeled "Hypothesis 2 (interaction)" in Figure 1). This hypothesis is intended to account for the emotional response that is part of the appraisal process (Scott et al., 2013).

Data and methods

Data collection and measures

Our analysis is part of a larger study evaluating the effectiveness of using aCASI technology (audio Computer-Assisted Self-Interview) plus adherence care manager support to improve patient adherence to ARVs compared with adherence information alone (McInnes et al., 2012). This study began in 2009 and was approved by the Boston University and Edith Nourse Rogers Veterans Memorial Hospital Institutional Review Boards. Data for our analysis come exclusively from the pre-randomization enrollment period (a 4-week period beginning on the 14th day after enrollment) of the larger study. Study participants were recruited by practitioners and recruitment staff at three large metropolitan medical centers, including two U.S. Department of Veterans Affairs (VA) hospitals (one on the east coast, and one on the west coast) and one public safety-net hospital (on the east coast). Eligible participants were HIV-positive, and either beginning or continuing ARVs. After the consent process, participants completed an enrollment questionnaire that identified self-reported adherence, demographic and health utilization information, substance and alcohol abuse, and relevant lifestyle factors, as well as symptom declaration paired with "bothersomeness" of symptoms and attribution of symptoms to HIV medications. Also at the study enrollment, participants were each given one electronic medication monitoring pill bottle (Medication Event Monitoring System, or MEMS) and were instructed to place the one HIV medication they took the most frequently (if more than one) into the bottle. Patients then brought the bottle for adherence data downloads to each subsequent clinical visit.

Dependent Variable.—Data for determining adherence came from the MEMS cap raw data. Adherence was calculated as the fraction of prescribed doses taken based on data for the 4-week period beginning on the 14th day after enrollment. The first 14 days following enrollment were ignored because patients had just received the MEMS caps and were starting to get used to this modification to their medication-taking. Days on which a patient was not able to access the pill bottle (due to hospitalization or incarceration, loss of the MEMS cap, or trouble downloading the data from the MEMS cap) were ignored; all other days were considered monitored. As long as a patient had any monitored days, the adherence measure was considered valid. Some study participants enrolled but had no monitored days in the relevant period despite receiving a MEMS cap (n=62).

Key Independent Variables.—At the study enrollment visit, participants answered survey questions about 20 symptoms common among patients with HIV. Participants were first asked whether or not they had experienced a specific symptom in the past four weeks (yes/no) (e.g., “In the past four weeks have you had nausea or vomiting?”). Then, for each symptom they experienced, participants were asked how much they were bothered by that symptom. Categorical responses included “it doesn’t bother me”, “it bothers me a little”, “it bothers me”, and “it bothers me a lot”. Finally, participants were asked whether they believed each symptom was a side effect of their ARVs (yes/no). Because of their known prevalence as side effects of ARVs, our analyses focus on the GI symptoms that were included in the survey: nausea, bloating, and diarrhea.

Control Variables.—The *demographic variables* in our analysis included gender, race, ethnicity, age, education, and HIV risk factor. Gender and Hispanic ethnicity were dichotomous variables. Race was categorized as Black, White, and other race, and age was calculated as a quantitative variable. Education was a dichotomous variable categorized as “high school or less” and “more than high school”. HIV risk factors were captured through two dichotomous variables: men who have sex with men (MSM) and intravenous drug users (IVDU). We also included *mental health and substance use disorder variables* in our model. Alcohol use was assessed with the Alcohol Use Disorders Identification Test Consumption (AUDIT-C) (Bradley et al., 2007): males with an AUDIT-C score of 4 or greater and females with an AUDIT-C of 3 or greater were considered to have a problem of alcohol abuse. Depression was categorized into no depression, minimal depression, mild depression, moderate depression, moderate/severe depression, and severe depression (Kroenke, Spitzer, & Williams, 2001). A comorbidity score was computed as the number of conditions indicated by the patient from a list of 20 conditions. We also controlled for *HIV-related variables*. A dichotomous variable compared patients who were continuing on ARVs at the time of the study to patients who were new to ARVs during the study period. ARV regimen was categorized into three variables: Protease-based, NNRTI-based, and Other. Medication complexity was recorded as the number of HIV medications in the patient’s ARV regimen. Another three variables captured low CD4 count (i.e., 0–200), medium CD4 count (i.e., 201–500), and high CD4 count (i.e., 500 or higher). Finally, patients’ *study site* is categorized into east coast VA hospital, east coast public hospital, and west coast VA hospital. These control variables were selected after a review of the literature indicated that they tend to be related to antiretroviral adherence.

Analytic strategy

Descriptive summaries were computed for the variables used in this study. T-tests were performed to compare the mean adherence between those patients with GI symptoms who attributed the symptom to ARVs with the adherence of those patients who did not attribute the symptom to ARVs (H1). Finally, multiple least-squares regressions of ARV adherence on bothersomeness of the symptom (H2) and covariates were performed. ARV daily adherence averaged over four weeks, which by the central limit theorem is approximately normally distributed, can be treated as a quantitative response in least-squares modeling (Tabachnik & Fidell, 2007). Significance of individual effects was determined through t-tests of the coefficients, and significance of the simultaneous effect of several variables was assessed through partial F-tests.

Results

Descriptive summaries of variables used in the study

The sample size for our analyses was 235. The reduction of this number from 297 was due to lack of sufficient MEMS data for 62 participants during our calculation window of adherence (i.e., the 4-week period beginning on the 14th day after enrollment). Table 1 presents the means and percentages of the dependent variable (adherence) and the sample characteristics that were used as covariates in our models. On average, patients in this sample were moderately adherent to their ARVs. The majority of the sample consisted of Blacks/African Americans and males, the average age was 51 and ranged from 23–86, most had more than high school education (58%), 36% were MSM, and 24% reported IVDU. With respect to mental health and substance use disorder, 26% reported alcohol use, the mode category for depression was “minimal”, and co-morbidity was common in this sample. Most patients were continuing ARVs at the time of the study. The majority of the sample was also on Protease-inhibitor based regimens, and the average number of medications in a regimen was about 2. In addition, a majority of the patients had a medium CD4 count. Finally, the sample was split nearly in half between the VA sites and the East Coast public hospital.

Table 2 shows the prevalence, bothersomeness, and attribution of GI symptoms (diarrhea, bloating, and nausea) in our sample of 235 patients. As this table shows, bloating and diarrhea were more common than nausea among this sample, and it was relatively common for patients to attribute these symptoms to their ARV medications. Patients who reported bloating were slightly more bothered by this symptom than patients with nausea or with diarrhea. In sum, nausea was the least common symptom of the three, but was most frequently attributed to ARVs. The number of patients reporting bloating and diarrhea was about equal, but bloating was slightly more bothersome, whereas diarrhea was more frequently attributed to ARVs.

The relationship between symptom attribution and adherence

To test the relationship between symptom attribution and adherence, we first conducted t-tests to compare mean adherence to ARV medications by whether a patient attributed the symptom to those medications or not. Results from these analyses are shown in Table 3. The

only symptom showing a statistically significant difference in mean adherence by symptom attribution to ARVs was diarrhea. This finding lends some support to our first hypothesis that patients will have worse adherence when they attribute a symptom to ARVs, at least for patients who reported having diarrhea, but not for patients who reported bloating or nausea.

To further test this relationship between attributing diarrhea to ARVs and adherence, we fit two regression models (see Table 4). The first model tests whether the significant difference in adherence observed between patients who attributed diarrhea to ARVs and those who did not remains after holding covariates constant. There were 81 patients who reported diarrhea as a symptom (see Table 3). This number was reduced to 79 in the final analysis due to missing data. As shown in Table 4, after controlling for covariates, patients who attributed diarrhea to their ARVs had statistically significantly worse adherence than patients who did not attribute diarrhea to their ARVs. In addition, relative to patients who reported diarrhea but were not bothered by it, patients who had diarrhea and were bothered by it had significantly worse adherence.

To test our second hypothesis, we included the interaction of attribution and bothersomeness into our models. The inclusion of these terms accounted for a modifying effect of symptom bothersomeness on the relationship between attribution and adherence. Partial F-tests for the inclusion of the interaction effects did not show significant interactions between attribution and bothersomeness.

Discussion

Our analyses provide support for our first hypothesis, but only among patients who reported experiencing diarrhea: holding covariates constant, patients who attributed diarrhea to ARVs had significantly worse adherence than those who did not attribute the symptom to ARVs. In testing for a moderating effect of bothersomeness on the relationship between attribution and adherence, we failed to reject our second null hypothesis.

The findings from this analysis have implications for the clinical encounter. Often, the physician will ask the patient about whether they are taking their ARVs as prescribed, remind them of the importance of adherence, and ask about any symptoms the patient has been experiencing. If physicians were aware that some patients are attributing symptoms to their HIV medications, they can have conversations with their patients to clarify what the symptoms are likely caused by and also make suggestions for strategies to cope with side effects. Our results suggest patients with diarrhea would benefit from this approach. Physicians may prescribe medications to slow the gut and reduce diarrhea in an effort to promote ARV adherence, or if the diarrhea is severe, the physician and patient could discuss alternative ARV regimens. Provider influence on patient understanding of the relationship between symptom attribution and adherence is a topic worthy of additional research, and may lead to strategies for increasing levels of ARV adherence.

The finding of a relationship between side-effect attribution and adherence only for diarrhea, and not nausea or bloating may also be because diarrhea is a more socially concerning and stigmatizing symptom than other side effects (Moutier, et al., 2009; Sayles et al., 2007;

Siddiqui et al., 2007). In the face of a serious and socially isolating problem like diarrhea, patients may more readily seek out symptom explanations that are potentially rectifiable (Sayles et al., 2007), such as attributing the symptom to medications as opposed to the underlying incurable disease. It is also possible that our sample of patients was not large enough to detect potentially small but real effects for the other symptoms we explored.

The lack of findings for the influence of bothersomeness on adherence also warrants some discussion. Overall, there was not much variation in our sample around bothersomeness of the symptoms, and the overall bothersomeness is somewhat mild. This lack of variation may have limited our ability to capture a relationship between bothersomeness and adherence. Another potential explanation is that nuances of “bothersomeness” were not captured by our survey instrument. Asking the patient “how much were you bothered by symptom ‘x’” was more open to interpretation than if we had asked “how much did symptom ‘x’ interfere with your ability to ‘y’”. Future studies should consider asking a battery of items regarding the degree to which a symptom impacts a variety of factors related to daily living (e.g., ability to work, do household chores, etc.).

There are noteworthy limitations of this study. Given the characteristics of the study sites that we recruited our sample from, our sample was over 80% male and also enriched with military veterans. Similarly it is likely that our sample had disproportionate numbers of patients of lower socio-economic status, although this was not assessed. Our sample is generally reflective of the older, heavily treated population of individuals living with HIV in the U.S., but our findings may not be generalizable to other settings and populations, such as women, patients receiving care at smaller health care centers, and higher income patients. Additionally, most of our sample (97%) had been on ARVs for some time prior to entering the study, and so it is unclear if these findings would hold in a population of patients initiating ARV for the first time.

In sum, our findings are consistent with the conceptual model we used which posits that when patients discern that a symptom is the result of their medication, they adjust their behavior as a coping strategy. This attribution to the medications seems to be more important for adherence than bothersomeness of that symptom. This conclusion has important implications for misattribution. For example, Swan (2015) found that illicit drug users reported sometimes attributing symptoms to that drug use, rather than disease. A patient may incorrectly attribute their symptom to ARVs, rather than something else that may be causing the symptom, which could have implications for their adherence. Incorporating patient beliefs about causes of symptoms and side-effects into the clinical encounter may contribute to improved symptom and medication management, and to better ARV medication adherence.

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Figure 1.
Conceptual Model on the Relationship between Symptom Attribution, Bothersomeness and Adherence (modified from Scott et al. 2013)

Table 1.

Sample Characteristics (N=235)

Variable	Mean (SD)/Percent
<i>Dependent Variable</i>	
Adherence to ARVs	.76 (.29)
<i>Demographic Variables</i>	
Male	81%
Race	
Black	57%
White	29%
Other race	14%
Hispanic	15%
Age	51 (9.99)
More than high school	58%
Man who has Sex with Men (MSM)	36%
Intravenous Drug User (IVDU)	24%
<i>Mental Health/Substance Use Disorder Variables</i>	
Alcohol use	26%
Depression	
No depression	23%
Minimal depression	31%
Mild depression	25%
Moderate depression	11%
Moderate/severe depression	8%
Severe depression	3%
Comorbidity score	2.03 (2.03)
<i>HIV-related Variables</i>	
Continuing on ARVs	97%
Medication regimen	
Protease-based ARV regimen	63%
NNRTI-based ARV regimen	32%
Other ARV regimen	5%
Number of HIV meds in ARV regimen	2.39 (1.00)
CD4 count	
Low	12%
Medium	53%
High	36%
<i>Study Site</i>	
East coast VA hospital	23%
East coast public hospital	54%

Variable	Mean (SD)/Percent
West coast VA hospital	23%

Note: ARV = antiretroviral; VA = Veterans Affairs.

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Table 2.

Prevalence, attribution, and bothersomeness of GI symptoms (N=235)

	Diarrhea	Bloating	Nausea
Prevalence [% (n) of study participants]			
has symptom	35% (81)	36% (82)	17% (38)
Attribution [% (n) of those who have symptom]			
attributes to ARVs	57% (46)	48% (39)	58% (22)
Degree of Bothersomeness [% (n) of those who have symptom]			
not bothered	14% (11)	6% (5)	13% (5)
a bit bothered	37% (30)	45% (37)	37% (14)
bothered	28% (23)	28% (23)	34% (13)
very bothered	21% (17)	21% (17)	16% (6)

Table 3.

Mean (SD) Adherence by Attribution of a GI Symptom to ARVs (N=235)

	Diarrhea (n=81)	Bloating (n=79)	Nausea (n=37)
Attribute to ARVs	.62 (.36) n=46	.67 (.36) n=39	.71 (.37) n=22
Do not attribute to ARVs	.85 (.26) n=35	.74 (.34) n=40	.81 (.25) n=15
Difference in Mean Adherence	-.23 *	-.07	-.10

Note: ARV = antiretroviral.

*
p=.001

Table 4.

Multiple regression results for patients with Diarrhea (n=79): Adherence regressed on Attribution, Botheredness, and Demographics

Variables	Model Coefficient (SE)
Intercept	1.049 (.362)
<i>Key Independent Variables</i>	
Attribution of diarrhea to ARVs	-.311 (.090) **
A bit bothered by diarrhea ¹	-.087 (.134)
Bothered by diarrhea ¹	-.308 (.142) *
Very bothered by diarrhea ¹	.033 (.170)
<i>Individual Characteristics</i>	
Male	.113 (.118)
Black ²	-.090 (.179)
White ²	-.069 (.177)
Hispanic	-.090 (.148)
Age	.001 (.004)
More than high school	.081 (.088)
Man who has Sex with Men (MSM)	.042 (.092)
Intravenous Drug User (IVDU)	.017 (.096)
<i>Mental Health/Substance Use Disorder Variables</i>	
Alcohol use	.086 (.086)
Minimal depression	.224 (.161)
Mild depression	.052 (.150)
Moderate depression	.162 (.166)
Moderate/severe depression	.099 (.192)
Severe depression	-.073 (.266)
Comorbidity score	-.016 (.025)
<i>HIV-related Variables</i>	
Continuing on ARVs	.046 (.195)
Protease-based ARV regimen ³	-.196 (.117)
Other ARV regimen ³	.222 (.285)
Number of HIV meds in ARV regimen	.075 (.060)
Low CD4 count ⁴	-.209 (.144)
Medium CD4 count ⁴	-.050 (.088)
<i>Study Site⁵</i>	
East coast VA hospital	-.150 (.116)
West coast VA hospital	.045 (.123)

Variables	Model Coefficient (SE)
R ²	.464
Adjusted R ²	.181

Note: ARV = antiretroviral.

*
p<.05

**
p<.001

Reference categories are:

¹ Not bothered by diarrhea;

² Other race;

³ NNRTI-based regimen;

⁴ High CD4 count;

⁵ East coast public hospital