

Mechanisms for the Negative Effects of Internalized HIV-Related Stigma on Antiretroviral Therapy Adherence in Women: The Mediating Roles of Social Isolation and Depression

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Background: Internalization of HIV-related stigma may inhibit a person's ability to manage HIV disease through adherence to treatment regimens. Studies, mainly with white men, have suggested an association between internalized stigma and suboptimal adherence to antiretroviral therapy (ART). However, there is a scarcity of research with women of different racial/ethnic backgrounds and on mediating mechanisms in the association between internalized stigma and ART adherence.

Methods: The Women's Interagency HIV Study (WIHS) is a multicenter cohort study. Women living with HIV complete interviewer-administered questionnaires semiannually. Cross-sectional analyses for the current article included 1168 women on

ART for whom data on medication adherence were available from their last study visit between April 2013 and March 2014, when the internalized stigma measure was initially introduced.

Results: The association between internalized stigma and self-reported suboptimal ART adherence was significant for those in racial/ethnic minority groups (AOR = 0.69, $P = 0.009$, 95% CI: 0.52 to 0.91), but not for non-Hispanic whites (AOR = 2.15, $P = 0.19$, 95% CI: 0.69 to 6.73). Depressive symptoms, loneliness, and low perceived social support mediated the association between internalized stigma and suboptimal adherence in the whole sample, as well as in the subsample of minority participants. In serial mediation models, internalized stigma predicted less-perceived social support (or higher loneliness), which in turn

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predicted more depressive symptoms, which in turn predicted suboptimal medication adherence.

Conclusions: Findings suggest that interconnected psychosocial mechanisms affect ART adherence, and that improvements in adherence may require multifaceted interventions addressing both mental health and interpersonal factors, especially for minority women.

Key Words: adherence, stigma, depression, social support, loneliness

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INTRODUCTION

Despite the importance of HIV medication adherence for effective treatment of HIV,¹ population-based estimates in the United States (US) indicate suboptimal levels of adherence to antiretroviral therapy (ART).^{2–4} An increasing body of literature from a variety of geographic and cultural settings suggests that HIV-related stigma is a psychosocial factor negatively associated with HIV medication adherence.^{5,6} Several dimensions of HIV-related stigma have been explored within this context, including enacted stigma (past experiences of discrimination) and perception of stigmatization in the community.^{7–9} Internalization of these stigmas, or acceptance of stigmatizing beliefs that are present in the community—and feelings of shame and lower self-worth as a consequence—may be the crucial factor in the stigma–adherence association.^{10–13} Psychosocial consequences of HIV-related internalized stigma (ie, self-imposed exclusion, avoidance, fears of rejection, social withdrawal, and depression) are hypothesized to play a major role in inhibiting a person's ability to adhere to HIV treatment.^{11,12,14,15}

Longitudinal studies in resource-limited settings in Uganda have suggested that internalized stigma predicts decreased levels of perceived social support and separately increase in depressive symptom severity.^{16,17} Research also suggests that loneliness and lack of perceived social support are associated with depressive symptoms among persons living with HIV.^{18,19} Furthermore, meta-analyses and systematic reviews also support the notion that internalized HIV-related stigma,⁶ lack of social support,²⁰ and depressive symptoms²¹ predict suboptimal ART adherence.

Despite the mounting evidence for the negative effects of internalized HIV stigma, few US studies have investigated whether loneliness, social support, depression, or related psychosocial factors operate as *mediating mechanisms* for the negative effects of internalized HIV stigma on medication adherence. It is important for the field of HIV research to understand why or how internalized stigma leads to nonoptimal adherence.²² At the present time, only a few studies explored mediating mechanisms in this relationship in the USA.^{15,23–25} Rao et al reported that the effect of internalized and enacted stigma on medication adherence is mediated by depression. Sayles et al reported an indirect effect between a multidimensional measure of internalized stigma and medication adherence that was mediated by mental health. Findings by DiIorio et al suggested that the relationship between stigma and adherence is mediated by self-efficacy and depression. Helms et al¹⁵ reported that interpersonal worries mediated the effect of internalized stigma on adherence.

However, studies examining depression used HIV stigma scales assessing internalized stigma in combination with other dimensions of stigma (eg, perceptions of stigma in the community, disclosure concerns, enacted stigma). Although internal and external stigma are intrinsically linked,¹⁴ internalized stigma is acceptance that the external stigma is justified and applies to the self, making people living with HIV feel that they have a tarnished character. The other dimensions of stigma, on the other hand, typically involve interpersonal experiences and perceptions of other people's attitudes. Internalized stigma appears to operate differently from other dimensions of HIV stigma on indicators of affective and behavioral health and well-being.¹² Thus, internalization of stigma may differentially predict depressive symptoms and adherence behavior as compared to other dimensions of stigma. Research in this area may develop a theoretical understanding of these relationships by distinguishing between pure internalized stigma scales and other dimensions of stigma. Furthermore, the existing literature has not yet elucidated whether and how multiple psychosocial constructs may work together to affect the relationship between internalized stigma and adherence in a single model.

Additionally, given epidemiologic reports that depression is more prevalent among women than men^{26,27} and that depressive symptoms are related to neighborhood racial/ethnic composition and racial discrimination,^{28,29} it is important to identify whether these factors have similar consequences for adherence in samples not consisting of predominantly male²⁵ and Caucasian samples of patients.²³ Empirical evidence also suggests that there are race and gender disparities in the likelihood of receiving social support and in the effects of social support on health.^{30–32} Moreover, black and other racial/ethnic minority women are disproportionately affected by HIV infection in the USA,³³ and the burden of HIV among minorities is exacerbated by disparities in levels of ART adherence by race/ethnicity and gender.^{3,34,35} Therefore, potential predictors of adherence may operate differently within a more diverse sample.

The purpose of the present study was to test whether social isolation (loneliness and lack of social support) and depressive symptoms mediate the relationship between internalized stigma and HIV medication nonadherence in a large sample of racially diverse women living with HIV across the USA. We also examined whether these associations differ by race. Given that several separate studies provided support for the theoretically plausible links between internalized stigma and higher social isolation; higher social isolation and depressive symptoms; and depressive symptoms and ART non-adherence; we hypothesized a serial mediation model: internalized stigma → higher social isolation (higher loneliness or lower social support) → depressive symptoms → ART nonadherence. This model posits a chain effect of internalized stigma on nonadherence sequentially through loneliness (and lower social support) and higher depressive symptoms: Internalized stigma may lead to social isolation (a potential interpersonal manifestation of feelings of lower self-value), which may lead to depressive symptoms that may subsequently be associated with nonoptimal adherence.

METHODS

Participants and Procedures

Participants were women living with HIV enrolled in the Women's Interagency HIV Study (WIHS), a multicenter longitudinal cohort study.^{36,37} As part of this ongoing cohort study, women living with HIV complete detailed interviewer-administered questionnaires, physical examinations, and specimen collection semiannually. Analyses for the current article included 1168 women currently on ART for whom data on medication adherence were available from their last study visit between April 2013 and March 2014 (which excludes 149 women from the analyses), when a measure of internalized stigma was initially added to the battery of measures. Data were collected from 9 WIHS sites in various regions of the United States—San Francisco/Bay Area, CA; Bronx/Manhattan, NY; Brooklyn, NY; Washington, DC; Chicago, IL; Atlanta, GA; Chapel Hill, NC; Miami, FL; and Birmingham, AL/Jackson, MS. Participants provided written informed consent and were compensated for participation. This protocol was approved by the Institutional Review Board at each study site's institution and by the WIHS Executive Committee. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

Measures

Adherence

HIV medication adherence was assessed by self-report of how often participants took their HIV medication as prescribed over the past 6 months (1 = 100% of the time; 2 = 95–99% of the time; 3 = 75–94% of the time; 4 = <75% of the time; 5 = I haven't taken any of my prescribed medications). Self-report measures of ART adherence have exhibited validity and reliability as a marker of clinical impact.^{38–40} A 95% ART adherence rate has been used as the cutoff for optimal versus suboptimal adherence in previous studies.^{41,42} Thus, we created a single variable, dichotomized at 95% or higher versus lower than 95%.

Internalized HIV-Related Stigma

Internalized *HIV-related* stigma was assessed with the negative self-image subscale of the revised HIV Stigma Scale⁴³ adapted from Berger et al.⁴⁴ This subscale includes 7 items rated on a 4-point scale (strongly disagree to strongly agree). A sample item is "I feel I'm not as good as others because I have HIV/AIDS". This scale showed high internal consistency and test-retest reliability in previous studies.^{45,46} Cronbach's alpha reliability coefficient for the 7-item subscale was 0.91 in the current sample.

Depressive Symptoms

The 20-item Center for Epidemiological Studies Depression (CES-D) scale⁴⁷ is used to assess depressive symptoms in the WIHS. Response options range from 0 to 3 (0 = Rarely or None of the Time, 3 = Most or Almost All the Time). Depressive symptoms, as measured by the CES-D,

have been shown to predict adherence in previous studies.^{48,49} The sum of the 20 items was used to assess depressive symptoms. The CES-D shows strong reliability in other literature,^{48,49} and in the present sample, Cronbach's alpha was 0.91.

Social Isolation (Social Support and Loneliness)

A shortened 15-item version of the MOS Social Support Survey⁵⁰ was used to assess social support. The rating scale ranged from 1 (None of the time) to 5 (All of the time), where higher scores indicate more social support. The Cronbach's alpha was 0.97 in the current study. A shortened 3-item version of the R-UCLA Loneliness Scale⁵¹ was used to assess loneliness. The rating scale ranged from 1 (Hardly ever) to 3 (Often), where higher scores indicate more social isolation. The R-UCLA Loneliness Scale has evidence of moderate-to-high reliability from other studies.^{52,53} Cronbach's alpha in the current sample was 0.85.

Data Analyses

We used descriptive statistics to examine the characteristics of the sample. To examine predictors of adherence, logistic regression analysis was conducted. The predictors were internalized stigma and covariates that previous research identified as important when examining stigma-adherence associations: race, age, time on ART, injected and noninjected drug use, income, and education. Adjusted odds ratios (AOR) controlling for these covariates were reported. A mediation model was used to test whether the association between internalized stigma and HIV medication adherence could be explained by depressive symptoms, social support, and loneliness using the mediation analysis with the bootstrap method for dichotomous outcomes developed by Hayes.⁵⁴ Serial mediation analyses examined the effects of internalized stigma on adherence through the pathways of a series of mediators.⁵⁴ These mediation analyses test the indirect effects of a predictor variable on outcomes through the mediator(s). We also conducted sensitivity analyses using medication adherence as a continuous dependent variable in multiple regression models. In these analyses, bootstrapping was used to accommodate the non-normal distribution of the adherence variable. All analyses were performed using SPSS (version 20).

RESULTS

Demographic and patient characteristics of the 1168 study participants are presented in Table 1. Over 88% of the participants were from racial/ethnic minority groups (blacks, Hispanics, and others), whereas non-Hispanic whites comprised only 12% of the sample. Given this distribution and the focus of the present study on marginalized minority groups in the USA, we used a dichotomized race variable in our analyses to compare non-Hispanic whites with all other racial/ethnic groups (Results were very similar when the 4-category race variable was used instead of the dichotomous race variable to examine the effect of stigma on adherence). The logistic regression models revealed that internalized HIV

TABLE 1. Descriptive Statistics for the Study Sample (N = 1168)

Variable	n (%)
Race	
Non-Hispanic white	139 (11.9)
Non-Hispanic black	788 (67.5)
Hispanic	200 (17.1)
Other	41 (3.5)
Noninjected drug use	256 (22.0)
Injection drug use	10 (0.9)
Adherence (<95%)	201 (17.2)

Variable	Mean (SD)	Possible Range
Age (yrs)	49.12 (8.59)	—
Education	4.09 (1.05)	1–7
Income	3.37 (2.14)	1–8
Years on ART	11.08 (6.30)	—
Internalized HIV-related stigma	1.74 (0.62)	1–4
Depressive symptoms	12.23 (11.27)	0–60
Social support	4.01 (1.02)	1–5
Loneliness	1.40 (0.59)	1–3

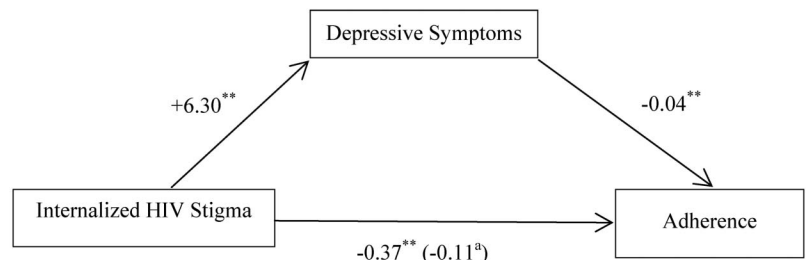
stigma was a significant predictor of nonoptimal adherence (AOR = 0.76, *P* = 0.042, 95% CI: 0.58 to 0.99). In this analysis, income, education, and injection drug use were not significant predictors (all *P* values >0.24), whereas being non-Hispanic white, of older age, having less time on ART, and not using noninjection drugs predicted better adherence (all *P* values <0.02). When we added the interaction between internalized stigma and race, the interaction term was also a significant predictor of adherence (AOR = 3.38, *P* = 0.026, 95% CI: 1.16 to 9.88). Therefore, logistic regression analyses were repeated for each race category separately. For the smaller sample of non-Hispanic whites, the effect was: AOR = 2.15, *P* = 0.188, 95% CI: 0.69 to 6.73. For women in racial/ethnic minority groups, the effect of internalized stigma on worse adherence was: AOR = 0.69, *P* = 0.009, 95% CI: 0.52 to 0.91. Based on this regression equation, we calculated the predicted probability for optimal adherence for

a person who has an average level (ie, equal to the sample mean) of internalized stigma (and average levels on all covariates), which yielded a predicted probability of 0.61. In comparison, the predicted probability of optimal adherence for a person whose internalized stigma is one point lower than the sample mean was 0.66.

Therefore, we examined the mediation hypotheses for the racial/ethnic minority group only (Results were very similar (with significant indirect effects for all mediation analyses) when analyses were conducted for the whole sample instead). In this subsample, logistic regression analysis revealed that internalized stigma was no longer a significant predictor of adherence when depression was added to the model (AOR = 0.89, *P* = 0.464, 95% CI: 0.66 to 1.21). Depression was a significant predictor of worse adherence in this model (AOR = 0.96, *P* < 0.001, 95% CI: 0.95 to 0.98). The mediation analysis yielded a significant indirect effect of internalized stigma on worse adherence through depression (*B* = -0.24, SE = 0.06, 95% CI: -0.37 to -0.14). Thus, the effect of internalized stigma on adherence was mediated by depression as demonstrated in Figure 1.

Some of the items in the depression scale concern low self-worth [eg, “I felt I was just as good as other people (reversed)”] and may inflate associations with internalized stigma. Therefore, we also tested the mediation effect among minority women using the sum of only those items in the depression scale that are unrelated to low self-worth, which again revealed a significant indirect effect of internalized stigma on adherence through the pathway of depression (*B* = -0.21, SE = 0.05, 95% CI: -0.32 to -0.11). Social support was also a significant mediator of the effect of internalized stigma on lower adherence with a significant indirect effect (*B* = -0.098, SE = 0.042, 95% CI: -0.195 to -0.030). Finally, loneliness was also a significant mediator of the effect of internalized stigma on lower adherence with a significant indirect effect (*B* = -0.12, SE = 0.05, 95% CI: -0.23 to 0.02).

As seen in Figure 2, for minority women serial mediation analysis also yielded a significant indirect effect of stigma on lower ART adherence through less social support and through higher depression (*B* = -0.03, SE = 0.01,



Note. Associations are presented as path coefficients (unstandardized).

^a When depression is in the model.

* *p* < .05; ** *p* < .01

FIGURE 1. Depression mediates the effect of internalized HIV-related stigma on suboptimal medication adherence for racial/ethnic minority groups (ie, non-whites). n = 1029.

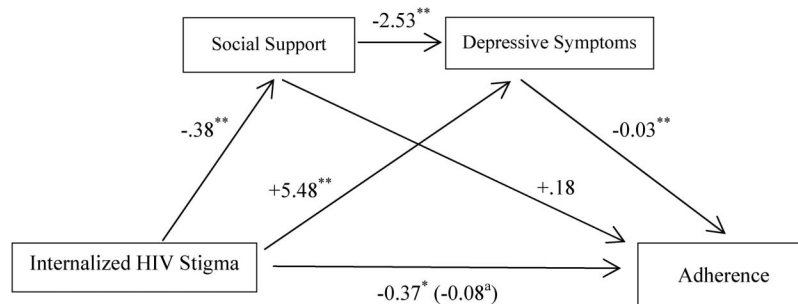


FIGURE 2. Serial mediation model in the association between internalized HIV-related stigma and suboptimal medication adherence for racial/ethnic minority groups (ie, non-whites). $n = 1029$.

Note. Associations are presented as path coefficients (unstandardized).

^a When social support and depression are in the model.

* $p < .05$; ** $p < .01$

95% CI: -0.06 to -0.01) (The serial mediation also yielded a significant serial indirect effect when the mean of the items in the depression scale that are unrelated to low self-worth were used). Figure 2 depicts the relationships between these variables, illustrating our findings that internalized stigma predicted less social support, which in turn predicted more depressive symptoms, which in turn predicted poorer medication adherence. Results were very similar when loneliness was used instead of social support in the analyses. The serial mediation also yielded a significant indirect effect of stigma on lower ART adherence through higher loneliness and through higher depression ($B = -0.07$, $SE = 0.02$, 95% CI: -0.12 to -0.02). Sensitivity analyses using adherence as a continuous dependent variable (using bootstrapping) are presented in Supplemental Digital Content 1, <http://links.lww.com/QAI/A788>. All of these analyses yielded results very similar to our original analyses using dichotomized adherence as the dependent variable.

DISCUSSION

The current study contributes to the extant literature by examining the mediating effect of social support or loneliness and subsequently, of depression, in the association between internalized HIV stigma and HIV medication adherence in women. The results indicate that HIV-related internalized stigma has an indirect and negative effect on adherence for women living with HIV mediated by social support or loneliness and depression. Initial analyses suggested that depressive symptoms, low social support, and loneliness each individually mediated the relationship between internalized stigma and poorer adherence. In further analyses, we found that less social support and separately higher loneliness operate through higher depression to mediate the relationship between internalized HIV stigma and lower adherence. These results were obtained for the whole sample, but the effect of internalized stigma on ART adherence was stronger for women in racial/ethnic minority groups than for non-Hispanic white women. This finding may contribute to our understanding of why non-white women living with HIV

have lower adherence rates and worse outcomes than white women.^{55,56}

The findings of the present study have important theoretical and practical implications. Our finding that depressive symptoms explain the relationship between HIV-related internalized stigma and medication adherence for women living with HIV support similar previous results from smaller samples consisting of mostly white men.^{23,25} Additional mechanisms through which stigma affects use of ART had yet to be elucidated, however. The current study indicated that less social support and higher loneliness may intensify depressive symptoms, which in turn predict poorer medication adherence. In general, this is in concordance with previous research suggesting that access to social support promotes ART adherence among people living with HIV by enabling them to overcome barriers to effective treatment.^{6,9}

At this point in stigma research, it is very important to understand in a more nuanced manner the ways in which stigma affects the lives of people living with HIV.²² The experience of internalizing stigma leads to self-imposed isolation and exclusion from social situations,^{17,57} which may lead to reduced self-efficacy and depressive symptoms such as disempowerment, helplessness, inability to concentrate, and feelings of negativity and anguish.^{14,47} It is likely that these symptoms make it more difficult to adhere to ART. The presence of depressive symptoms may even affect one's desire for self-preservation and thus contribute to the tendency to neglect self-care needs.⁴⁸ It is possible that these relationships also operate in a bidirectional manner. Existing literature suggests that effective ART adherence is associated with decreased depressive symptom severity.²¹ Depression could lead to lower social support, given that research suggests that nondepressed individuals show patterns of negative affect and a tendency to socially reject depressed individuals after a social interaction with them.⁵⁸ Furthermore, lower social support could lead to more internalized stigma, given that persons living with HIV often draw on social support to minimize the harmful influences of stigma.⁶

An understanding of these interconnected factors affecting HIV medication adherence provides insight into what conditions/situations can potentially be targeted through interventions. Our findings contribute to the existing literature by implicating multiple stages at which we may be able to intervene to improve HIV-related health outcomes (ie, 1—internalization of stigma; 2—lack of social support or loneliness; and 3—depression). Programs aiming to improve ART adherence for women living with HIV may benefit from targeted strategies to address all 3 of these factors. Some depression treatment interventions have yielded promising results in improving adherence,^{59,60} but others resulted in no effect.^{61,62} Future intervention studies should examine the effectiveness of programs that seek to address depression, internalized stigma, and lack of social support simultaneously.

The strengths of the current study include the use of detailed and reliable measurement tools—including a multi-item measure of internalized stigma specific to HIV that has shown good evidence of construct and discriminant validity⁴³—and measures of social support and loneliness not previously used to explore these relationships. Compared to previous studies,^{23,49} our study included a larger sample of racial/ethnic minority participants, who may be more representative of the population with least engagement in HIV care,⁵⁵ the highest risk of HIV mortality in the USA,⁵⁶ and according to the present results, may be more strongly affected by stigma. Furthermore, our sample was comprised of women living with HIV who represent multiple geographically diverse sites within the USA, rather than a single site, which may also enable greater generalizability. Finally, we used mediation modeling using bootstrapping to examine the interconnected relationships, which allowed us to explore the interpersonal and intrapersonal mechanisms in the association between internalized stigma and HIV medication adherence.

Limitations of the study include the use of cross-sectional data, which prevents us from inferring causal relationships. However, our study findings are consistent with previous research and theory, which suggests that constructs similar to internalized stigma, such as self-esteem, lead to depression longitudinally, but that prior depression does not predict later self-esteem.⁶³ Our findings also lend theoretical support to causal models of the relationships between internalized stigma and social support,¹⁷ and depression separately,¹⁶ found in longitudinal designs in Uganda. Future studies using longitudinal designs or interventions are required to further elucidate causal relationships between social support and depressive symptoms, as well as depressive symptoms and adherence, and to confirm our hypothesized directionality.

An additional limitation is that there may be unobserved variables that are associated with both the mediators and the outcome, which may lead to biased results. We controlled for some of the variables that are known to predict ART adherence. However, there may be other variables not measured in our study that are associated with both social support (or loneliness) and adherence. It is also possible that unobserved potential mediator variables

exist that are associated with our observed mediators and confound the mediation. These difficulties in interpretation are inherent in every mediation analysis because it is not possible to experimentally manipulate both the predictor and the mediator in a single study. Future research examining other theoretically relevant variables and using longitudinal designs may contribute to a better understanding of mediating mechanisms by providing analyses from different perspectives.

We examined predictors of adherence using a self-reported measure of adherence, which may be subject to response bias. Nevertheless, an extensive literature review indicated that brief self-reported measures of ART adherence such as that used in the current study are robust and reliable.³⁸ Future studies examining associations with ART adherence may consider use of objective markers of adherence, such as antiretroviral concentrations in hair samples.

Our findings suggest that internalized stigma and poor adherence are indirectly related. This relationship is mediated by lack of social support, loneliness, and depressive symptoms. Further research can use these findings to develop multifaceted interventions to help women living with HIV to obtain mental health treatment and/or build skills to deal with these social and psychological factors, and evaluate the impact of such interventions on adherence.

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