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Authors
Shin, Sanghyuk S
Carpenter, Catherine L
Ekstrand, Maria L
et al.

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Household Food Insecurity as Mediator of the Association between Internalized Stigma and Opportunistic Infections

Sanghyuk S. Shin,[1] Catherine L. Carpenter[2], Maria L. Ekstrand[3,4], Kartik Yadav[1], Saanchi V. Shah[2], Padma Ramakrishnan[5], Suresh Pamujula[6], Sanjeev Sinha[5], Adeline M. Nyamathi[1,2]

Author affiliations: [1]Sue & Bill Gross School of Nursing, University of California Irvine, USA [2]Department of Epidemiology, University of California Los Angeles, USA [3]University of California San Francisco, USA [4]University of California Berkeley, USA [5]Department of Medicine, All India Institute of Medical Sciences, India [6]A.C.Subba Reddy Govt. Medical College, Nellore, India.

Running head: Food insecurity as mediator of the association between stigma and HIV outcomes

Corresponding author and request for reprints:

Adey M. Nyamathi, ANP, PhD, FAAN

Founding Dean and Distinguished Professor

Sue & Bill Gross School of Nursing, University of California, Irvine

252D Berk Hall, Irvine, CA 92697

anyamath@uci.edu

Tel: (949) 824-8932

Fax: (949) 824-0470

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Abstract

Internalized HIV stigma can affect health outcomes, but the mechanism underlying this relationship is poorly understood. We investigated the potential pathways for the association between internalized stigma and opportunistic infections (OIs) among women living with HIV in rural India. We conducted a cross-sectional study involving in-person interviews with 600 participants. We modeled two outcome variables, total number of OIs and fungal dermatoses, which was the most frequently reported OI. Causal mediation analysis was performed to estimate the total effect, direct effect, and indirect effect through mediators while controlling for confounders. Food insecurity was a strong mediator of the association between internalized stigma and the number of OIs (70% of the total effect) and fungal dermatoses (83% of the total effect), while the indirect effect of stigma through adherence was minimal for both outcomes. Household food insecurity may be an important mediator of the impact of HIV-related stigma on opportunistic infections.

Keywords: Fungal infections; Dermatoses; Adherence; Antiretroviral therapy; Nutrition.

INTRODUCTION

Stigma is defined as a set of negative beliefs that society has about something or someone. Increasing evidence has established HIV stigma as a major driver of morbidity and mortality among HIV-infected persons (1–4)(1–4). Stigma has been shown to increase depression and loneliness, and reduce social support, which are strong predictors of poor adherence to antiretroviral therapy (ART)(1,5). Stigma may also affect physical health by increasing stress, which impairs the immune function (6–8). The effect of chronic stress on immune function may be exacerbated among HIV-infected persons (6–8).

The impact of stigma on health may be even more pronounced among women living with HIV. In many social settings globally, women are expected to conform to gender-defined moral traditions, including sexual purity. In such settings, HIV infection among women may be equated with immorality and failure to uphold traditional obligations (9,10). This can lead to delayed testing and treatment for HIV infection among women, resulting in adverse health outcomes, including opportunistic infections (OIs) (11).

While previous research on the health effects of stigma has focused primarily on adherence to ART, stigma may also increase household food insecurity among vulnerable populations living with HIV. In particular, internalized stigma, the acceptance of negative attitudes about HIV and themselves, may increase avoidance of social interactions due to feelings of shame, and reduced sense of self-worth and self-deprecation (12–14). This may have negative financial consequences, particularly among women, for whom social interaction is often critical for economic activity,

financial support, and food procurement (15,16). In addition, social avoidance due to internalized stigma could limit opportunities for benefiting from social programs for persons living with HIV (17).

A previous study of people living with HIV in Uganda found that internalized stigma was significantly associated with increased food insecurity among persons living with HIV (17). The authors posited that stigma could limit access to traditional social support, including borrowing food or money from relatives, leading to financial harm and food insecurity (17,18). Despite this, few studies have studied the impact of stigma on food insecurity and ART adherence and the subsequent development of OIs among women.

Food insecurity could affect HIV-related morbidity through multiple pathways (19). Food insecurity could cause undernutrition, including deficiencies in protein and energy intake, and micronutrient deficiency (20). Nutritional deficiencies adversely affect the immune system and, thus, increase the vulnerability opportunistic infections (21). Furthermore, weight loss due to undernutrition has been shown to exacerbate the catabolic state induced by HIV infection (22). The could lead to increased toxicity and reduced efficacy of HIV medication (22). Among HIV-infected patients, weight loss, reduced appetite, and decreased albumin concentrations are associated with high rates of OIs and death (22–24). In addition, food insecurity is associated with substantial psychosocial stress (19). The inadequate availability of food and the pressure of feeding the family may be particularly stressful for women (25). Stressful events have been shown to increase HIV disease progression (26). Taken together, evidence from

previous studies suggests that stigma may impact HIV outcomes through a pathway involving food insecurity, independent of ART use.

Improved understanding of the pathway by which HIV-related stigma impacts health outcomes could inform the development of interventions to reduce the health impact of stigma (1). We previously conducted a study of rural women living with HIV in India and found that the majority (94%) took 50% or less of prescribed ART in the past month (27). That study also found a non-linear association between adherence to ART and the number of OIs experienced during the past six months (27). Fungal dermatoses were the most common OIs and had the strongest association with ART adherence. In the present study, we aimed to build on these findings and expand the understanding of factors that affect OIs among HIV-infected women. We also examined fungal dermatoses as a secondary outcome given its high prevalence in our study population. Given the association between HIV-related internalized stigma and food insecurity shown in previous studies, we focused our analysis on whether this association is mediated through ART adherence and food insecurity (17,18).

METHODS

Design

A baseline survey was conducted among 600 women enrolled in a randomized controlled intervention trial (27). The aim of the parent study was to assess the impact of a community-based intervention on physical and psychological health outcomes of the mother and child at six, twelve and 18 months post enrollment. The study was approved by the University of California Los Angeles Institutional Review Board,

University of California Irvine Institutional Review Board, and the Ministry of Health Research Ethics Committee in India. All participants provided written informed consent prior to enrollment.

Sample and Setting

The study population was recruited by posting flyers in Community Health Centers and Primary Health Clinics (PHCs) in four sites in Nellore and Prakasam, rural districts in Andhra Pradesh, India. Informed consent was administered to women living with HIV/AIDS who met the following study eligibility criteria: a) age 18-50 years of age, b) diagnosed with HIV and receiving ART for three months or more, c) CD4 T-cell counts > 100 cells/mm^3, d) living with at least one of her children aged 3-8, e) not a participant of previous Asha Life Intervention or Phase I, and f) not a pregnant or lactating mother. All participants were receiving their medication at government-run ART clinics. The baseline questionnaire was administered face-to-face by interviewers who recorded the data on electronic tablets. Blood samples were collected and transported to a local clinical laboratory for testing. Enrollment into the prospective intervention study occurred in a serial fashion with 100 participants at a time.

Instruments

The majority of the instruments have been previously used with either rural or urban HIV-positive individuals in southern India (27,28). Sociodemographic information obtained included age, education, marital status, religion, number of children, and monthly income. Educational attainment was ascertained in 8 categories and then

grouped into the following categories: 1) no formal education; 2) 1 – 4 years; 3) 5 – 9 years; and 4) ≥ 10 years. Participants were asked to select their marital status from the following categories: 1) married, 2) never married/single, 3) divorced/separated, and 4) widowed. Each participant was asked the month and year that they were diagnosed with HIV to calculate the number of years living with HIV.

Opportunistic infections (OIs). The outcome of interest for this study was the total number of OIs in the past 6 months and the odds of fungal dermatoses, a non-inflammatory fungal skin condition. Participants were presented with a list of 8 OIs (e.g. tuberculosis, fungal dermatoses) and for each one, asked to indicate whether or not they had experienced it in the past 6 months. We summed the number of OIs reported for each participant.

HIV-related internalized stigma. We measured internalized stigma using a 8-item scale (29). This instrument contained five items on the extent to which respondents believe that they should avoid the following activities because they have AIDS: 1) holding a new infant; 2) feeding children; 3) sharing dishes or glasses; 4) cooking for other people; and 5) visiting people. In addition, the instrument included three items on the extent to which the feel the following about their AIDS status: 1) brought shame to their family; 2) they are paying for karma or sin; 3) makes them feel disgusting. Each item has a 4-point response scale ranging from 0 (not at all) to 3 (a great deal), with higher scores corresponding to increased stigma. Responses were averaged to create a scale score. This 8-item scale was adapted from a 10-item scale used in our prior studies with persons living with HIV in India (30). We removed two items with low correlation with the overall score ("How much do you feel that you have AIDS because

you have done wrong behaviors?" and "How much do you feel guilty about having AIDS?"). In the current sample, Cronbach's alpha was found to be 0.63 for the full 10-item scale and 0.79 after removing the two items.

Food insecurity. The Household Food Insecurity Access Scale (HFIAS) was used to measure food insecurity (31). The HFIAS consisted of 9 items that assessed the frequency in the past 4 weeks of worrying about not having enough food (1 item), and perceived insufficient quality (3 items) and quantity of food (5 items), due to a lack of resources. Response options range from 0 "Never" to 3 "Often", and were summed over all items. Cronbach's alpha for this scale was 0.82.

Adherence to ART. A self-reported measure assessed adherence to ART via a Visual Analogue Scale (VAS), in which participants were shown a line with numbered intervals between 0 and 100 and were asked to point to the spot on the line that best represented the percent of pills they took in the past month (32). This measure has been validated with Indian patients (33,34).

Statistical Methods

Interview data collected from electronic tablets by the interviewers were uploaded via internet to a data server located on the UCLA campus. Means and frequency distributions were utilized to check for errors and clean the data. We used R version 3.4.0 (The R Project for Statistical Computing; http:/www.r-project.org) for all analyses. In accordance with the American Statistical Association's recommendations on the use of *P* values, no significance threshold was used for statistical inference (35,36).

We developed a directed acyclic graph to guide our mediation analysis (Figure 1). The total effect is the effect of internalized stigma on the outcome (number of OIs and fungal dermatoses) and is composed of the direct effect and the indirect effects (37). The indirect effects are the effect of internalized stigma on the outcome through the mediating variables, food insecurity or adherence. The direct effect is the effect of internalized stigma on the outcome not through food insecurity or adherence to ART.

We first examined the association between mediators and two outcomes: 1) total number of OIs during the past six months and 2) fungal dermatoses. Generalized linear models (GLMs) with Poisson distribution and log link were fitted to model the number of OIs. GLMs with logit link were used for the binary outcome variable of fungal dermatoses (1 = Yes, 0 = No). The multivariable models for each outcome included both adherence (log_{10} transformed) and food insecurity along with the potential confounders mentioned above.

We performed generalized mediation analysis using the mma package in R (38,39). This approach involved modeling the change rate in the outcome variable when the exposure variable changes by a given unit (38,39). The estimated coefficients, in effect, are standardized and can be used to generate average estimates of the total, direct, and indirect effects, regardless of the scale of the outcome variable. GLM was used to model the relationship between variables as described above. The average total effect was calculated by taking the average change in the outcome for an increase of one internalized stigma score from 100 observations resampled with replacement from the dataset. Food insecurity and adherence were tested simultaneously as parallel mediators. For each mediator, we calculated the natural direct effect by first generating

a sample of each mediator based on its marginal distribution for the 100 resampled observations. Thus, mediators were allowed to vary naturally based on their relationship with internalized stigma and other covariates (38,39). The natural direct effect not through each mediator was then estimated by GLMs. Lastly, indirect effect for each mediator was calculated by taking the difference between the average total effect and the average direct effect not through the mediator. The bootstrap method with 500 replicates was used to determine the mean and 95% confidence intervals (CIs) for each effect estimate (38,39).

RESULTS

A total of 600 eligible participants were enrolled in our study. Participants were 34 years of age on average and had an average of two children (Table 1). About half of the participants were widowed (51%) and reported having no formal education (49%). Most participants reported belonging to the Hindu religion (73%).

The average score on the internalized stigma scale was 2.8 out of a maximum possible score of 3.0 (Table 1). Notably, over 90% of the participants reported agreeing “a great deal” with the statements “I should avoid holding an infant”, “I am paying for my karma/sins”, and “I feel disgusting”. The average food insecurity score was 21.1 out of a possible score of 27. Seventy-three percent of participants reported often worrying about not having enough food.

The average number of years since HIV diagnosis was 4 years, and the average percent adherence to ART over the past month was 30.4%. The average CD4+ T cell count was 447.4 cells/mm^3. Participants reported an average of nearly five OIs within

the past six months (Table 1). Fungal dermatoses were reported by 93% of the participants.

Association between food insecurity and HIV-related outcomes

We examined the association between food insecurity and health outcomes using GLMs with the number of OIs and fungal dermatoses as dependent variables (Figure 1; Table 2). Food insecurity was associated with an increase in OIs in the unadjusted model (incidence rate ratio [IRR] = 1.032 per +1 increase in food insecurity score; 95% CI = 1.016, 1.049) and in the model adjusted for internalized stigma and confounders (IRR = 1.029 per +1 increase in food insecurity score; 95% CI = 1.013, 1.045). Similarly, food insecurity was associated with increase in the odds of fungal dermatoses in the unadjusted model (OR = 1.296 per +1 increase in food insecurity score; 95% CI = 1.177, 1.428) and in the model adjusted for internalized stigma and confounders (OR = 1.281 per +1 increase in food insecurity score; 95% CI = 1.118, 1.466).

Association between adherence to ART and HIV-related outcomes

Adherence to ART was associated with a decrease in OIs in the unadjusted model (IRR = 0.865 per +1 increase in $\log_{10}$ adherence score; 95% CI = 0.766, 0.977) and in the model adjusted for internalized stigma and confounders (IRR = 0.906 per +1 increase in $\log_{10}$ adherence score; 95% CI = 0.833, 0.985; Table 2).

Adherence to ART was also associated with a decrease in the odds of fungal dermatoses in the unadjusted model (OR = 0.049 per +1 increase in $\log_{10}$ adherence

score; 95% CI = 0.011, 0.212) and in the model adjusted for internalized stigma and confounders (OR = 0.079 per +1 increase in $\log_{10}$ adherence score; 95% CI = 0.016, 0.402).

Direct and indirect effects estimated by causal mediation analysis

Internalized stigma was associated with number of OIs and fungal dermatoses in models without adjustment for mediators (Supplemental Table 1). Adjusting for mediators reduced the effect size for the association between internalized stigma and the outcomes.

Figure 2 shows the results of the mediation analysis for the relationship between internalized stigma and the number of OIs. We found a strong indirect effect through food insecurity, responsible for 70% of the total effect (Figure 2A, 2C). The indirect effect of internalized stigma on the number of OIs through ART adherence was minimal (3% of the total effect). The direct effect of internalized stigma on the number of OIs not through food insecurity or adherence was IRR = 1.058 (95% CI = 0.972, 1.166). The direct effect was responsible for an estimated 27% of the total effect, but with wide 95% CIs that overlap 0% (Figure 2A, 2C).

We found a strong indirect effect of internalized stigma on the fungal dermatoses through food insecurity, responsible for 83% of the total effect (Figure 2B, 2C). The indirect effect through adherence to ART was 12% of the total effect. We did not observe a direct effect of internalized stigma on the fungal dermatoses (Figure 2B, 2C).

DISCUSSION

In a large study of rural women living with HIV in India, we found that food insecurity was a strong mediator of the association between HIV-related internalized stigma and OIs. In contrast, reduced adherence to ART did not appear to mediate the association between internalized stigma and number of OIs and only minimally explain the association between internalized stigma and fungal dermatoses. Our findings are consistent with several previous studies that report the effect of internalized stigma on food insecurity and adherence to ART (1–5,17). However, to our knowledge, the role of these factors on mediating the relationship between internalized stigma and OIs has not been reported previously.

A previous study in Uganda found that stigma is a strong predictor of food insecurity due to reduced social support (40). We found that reduced food insecurity is, in turn, associated with OIs. This finding is consistent with studies of the relationship between food insecurity and HIV (19). For example, a previous study of people living with HIV in rural Uganda found that food insecurity was associated with lower CD4 counts, which persisted even after controlling for adherence to ART (11). Similarly, we found that food insecurity was independently associated with increased OIs and fungal dermatoses after controlling for confounding by education, age, and years since HIV diagnosis. These findings suggest that food insecurity may increase the risk of OIs through nutritional pathways (11).

While food insecurity was a strong mediator for the effect of HIV-related internalized stigma on health outcomes, our mediational analysis suggests that internalized stigma may affect the risk of OIs and fungal dermatoses directly or through other mechanisms. This finding is consistent with the psychosocial stress model, which

posits that the stress caused by stigma can directly cause poor health outcomes (3,5). Therefore, health interventions should be designed to address the direct effect of HIV-related internalized stigma while also focusing on countering the negative impact of stigma on food insecurity and adherence to ART.

Contrary to our expectation, poor adherence had a limited role in explaining the association between internalized stigma and health outcomes in our study population. It is possible that the mediating role of adherence may be minimal in highly vulnerable populations who experience multiple consequences of internalized stigma that impact health. In addition, ART adherence was very low in our study population, with limited variability. This may have reduced our ability to detect the role of adherence on mediating the stigma – OI relationship. Additional research in different populations and settings is needed to improve the understanding of the relationship between stigma and OIs.

Strengths of our study include our large sample size of highly vulnerable women living with HIV in rural India. Our large sample size allowed us to fit multiple models and generate robust estimates of the direct and indirect effects of internalized stigma on two HIV-related health outcomes. Our primary findings were consistent in models for both number of OIs and fungal dermatoses, which strengthens the confidence in our conclusions.

Our study was subject to several limitations. First, this was a cross-sectional analysis and as such we are not able to determine the temporality between the occurrence of our exposures and outcomes. Therefore, our findings may not reflect a causal relationship. To explore the alternate explanations of these relationships, we

constructed separate mediation models to determine whether internalized stigma might be a mediator of the association between food insecurity and OIs. The results did not support this alternate explanation (Supplementary Figure). Despite this, longitudinal studies should be conducted to draw stronger conclusions about causality. Second, we did not explore other determinants of food insecurity such as medical expenses, and enacted stigma leading to job loss and discrimination, which may require special attention (17). We also cannot rule out the possibility of residual confounding that may explain our findings, including possible lower access to health care among participants with higher levels of food insecurity. Third, our outcomes were self-reported by the participants and validation of diagnoses was not obtained from physicians. Therefore, our study is prone to misclassification bias. We also did not collect additional information that could illuminate the mechanism by which internalized stigma could affect food insecurity, including avoidance of social interaction and reduced economic activity. Future studies on this topic should address this gap.

Our findings have important implications for HIV care among vulnerable populations at high risk of adverse outcomes due to internalized stigma and food insecurity. We found that food insecurity and internalized stigma were experienced by a majority of women in our study population. Individual and population-level interventions are needed to reduce HIV-related stigma in India, and other similar settings. Healthcare professionals could serve as liaisons between people living with HIV and the community they live in so that they have a sense of belonging and receive compassionate care. Public health efforts should be channeled towards educating and counseling the entire community to develop a positive and caring attitude towards people living with HIV.

Given the high level of food insecurity found in our population, HIV programs in vulnerable populations should emphasize nutritional interventions as a fundamental component of HIV care along with interventions to reduce stigma and improve ART adherence (41). Social interventions, including initiation and development of income generating activities for women living with HIV may also help reduce food insecurity and contribute to improved health. Future longitudinal studies should build on our findings by confirming the role of food insecurity in mediating the pathway by which internalized stigma affects health outcomes and determine whether improving food security can reduce the adverse effects of internalized stigma.

CONCLUSIONS

Our study suggests that household food insecurity is a strong mediator between internalized stigma and two HIV-related health outcomes, number of OIs and fungal dermatoses. Interventions to address the adverse effects of internalized stigma should explore improving food insecurity in addition to improving adherence to ART. Longitudinal studies are needed to confirm our findings.

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Compliance with Ethical Standards

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures in this study were conducted in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments. This study was approved by the University of California Los Angeles Institutional Review Board, University of California Irvine Institutional Review Board, and the Ministry of Health Research Ethics Committee in India.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

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Table 1. Characteristics of participants

Characteristic	Mean (SD) or n (%)
Age in years	34.3 (7.0)
Education	
None	292 (48.7%)
1 – 4 years	98 (16.3%)
5 – 9 years	123 (20.5%)
≥10 years	87 (14.5%)
Religion	
Hindu	439 (73.2%)
Muslim	44 (7.3%)
Christian	117 (19.5%)
Marital status	
Married	238 (39.7%)
Divorced/separated	54 (9.0%)
Widowed	308 (51.3%)
Number of Children	1.9 (0.8)
Internalized stigma scale	2.8 (0.3)
Food insecurity score	21.1 (3.4)
Years since HIV diagnosis	4.1 (2.9)
Percent adherent to ART	30.4 (13.2)
CD4+ T cell count (cells/mm^3)	447.4 (273.6)
Number of OIs past 6 months	4.6 (1.2)
Fungal dermatoses	
No	40 (6.7%)
Yes	560 (93.3%)

Table 2. Associations between putative mediators of internalized stigma and HIV-related health outcomes (opportunistic infections and fungal dermatoses)

Mediator	Number of OIs as dependent variable IRR (95% CI)	*P*	Fungal dermatoses as dependent variable OR (95% CI)	*P*
Food insecurity				
Unadjusted model	1.032 (1.016, 1.049)	<0.001	1.296 (1.177, 1.428)	<0.001
Multivariable model[a]	1.029 (1.013, 1.045)	<0.001	1.281 (1.118, 1.466)	<0.001
Adherence to ART[b]				
Unadjusted model	0.865 (0.766, 0.977)	0.020	0.049 (0.011, 0.212)	<0.001
Multivariable model[a]	0.906 (0.833, 0.985)	0.020	0.079 (0.016, 0.402)	0.002

[a]Adjusted for age, education, years since HIV diagnosis, and internalized stigma
[b]Log_{10} transformed
Note: OI = opportunistic infections; ART = antiretroviral therapy; IRR = incidence rate ratio; OR = odds ratio

Supplemental Table 1. Association between internalized stigma and outcomes with and without mediators.

	Number of opportunistic infections IRR (95% CI)			Fungal dermatoses OR (95% CI)		
Characteristic	**Unadjusted**	**Adjusted (no mediators)**	**Adjusted with mediators**	**Unadjusted**	**Adjusted (no mediators)**	**Adjusted with mediators**
Stigma	1.236 (1.143, 1.337)	1.232 (1.131, 1.342)	1.063 (1.031, 1.095)	4.089 (3.220, 5.191)	3.833 (2.997, 4.901)	1.066 (0.525, 2.166)
Age (+1 years)	1.001 (0.999, 1.004)	1.001 (0.999, 1.003)	1.001 (0.999, 1.002)	1.012 (0.935, 1.095)	1.007 (0.949, 1.068)	0.997 (0.955, 1.040)
Education						
None	1.00	1.00	1.00	1.00	1.00	1.00
1 – 4 years	0.943 (0.910, 0.977)	0.949 (0.918, 0.980)	0.956 (0.927, 0.985)	1.214 (0.743, 1.983)	1.502 (0.916, 2.464)	1.813 (0.785, 4.185)
5 – 9 years	0.986 (0.918, 1.058)	0.988 (0.918, 1.064)	1.010 (0.940, 1.085)	1.326 (0.820, 2.144)	1.393 (0.918, 2.114)	1.827 (1.299, 2.569)
≥10 years	0.945 (0.903, 0.988)	0.937 (0.904, 0.972)	0.965 (0.918, 1.013)	1.383 (0.532, 3.597)	1.490 (0.607, 3.661)	1.680 (0.692, 4.082)
Months since HIV diagnosis (+1 month)	0.998 (0.988, 1.009)	1.001 (0.989, 1.013)	1.004 (0.994, 1.013)	0.911 (0.836, 0.992)	0.917 (0.839, 1.001)	0.958 (0.826, 1.112)
Adherence to ART[a]	0.865 (0.766, 0.977)	N/A	0.906 (0.833, 0.985)	0.049 (0.011, 0.212)	N/A	0.079 (0.016, 0.402)
Food insecurity score	1.032 (1.016, 1.049)	N/A	1.029 (1.013, 1.045)	1.296 (1.177, 1.428)	N/A	1.281 (1.118, 1.466)

[a]Log_{10} transformed

Note: OI = opportunistic infections; ART = antiretroviral therapy; IRR = incidence rate ratio; OR = odds ratio

Figure 1. Directed acyclic graph showing mediation pathways leading to opportunistic infections due to internalized stigma. Confounders include: Education, age, years since HIV diagnosis.

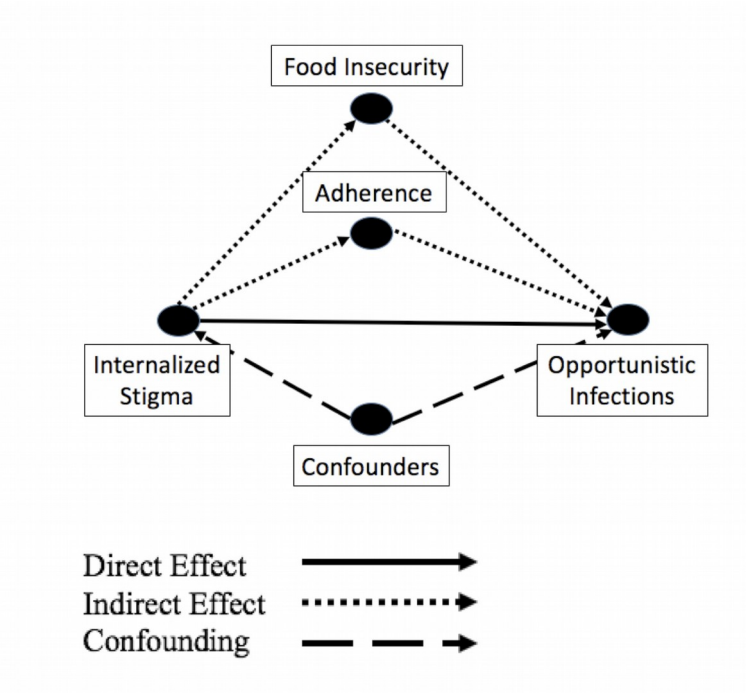
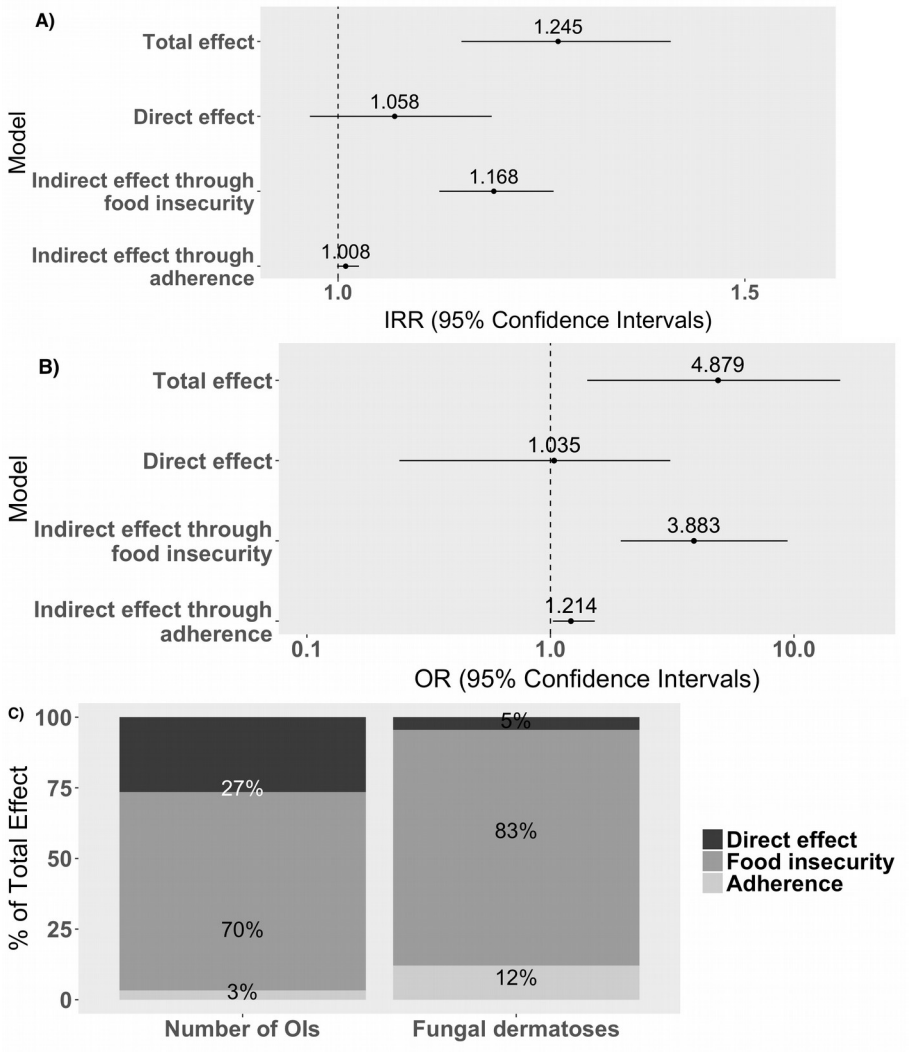


Figure 2. Total, direct, and indirect effects of internalized stigma on OIs. A) Effect of internalized stigma on the number of OIs. B) Effect of internalized stigma on fungal dermatoses. C) Percent of total effect on the number of OIs and fungal dermatoses for the direct effect of internalized stigma and the indirect effects through food insecurity and adherence to ART. Models were adjusted for age, education, and years since HIV diagnosis. IRR and OR estimates reflect change per +1 increase in internalized stigma score. OI = opportunistic infections; ART = antiretroviral therapy; OR = odds ratio; IRR = incidence rate ratio; CI = confidence intervals.



Supplemental Figure. Exploratory analysis of the association between food insecurity and OIs through internalized stigma and adherence. A) Effect of food insecurity on the number of OIs. B) Effect of food insecurity on fungal dermatoses. Models were adjusted for age, education, and years since HIV diagnosis. IRR and OR estimates reflect change per +1 increase in food insecurity score. OI = opportunistic infections; ART = antiretroviral therapy; OR = odds ratio; IRR = incidence rate ratio; CI = confidence intervals.