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Longitudinal assessment of associations between food insecurity, antiretroviral adherence and HIV treatment outcomes in rural Uganda

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Abstract

Introduction—Food insecurity is a potentially important barrier to the success of antiretroviral treatment (ART) programs in resource-limited settings. We undertook a longitudinal study in rural Uganda to estimate the associations between food insecurity and HIV treatment outcomes.

Design—Longitudinal cohort study.

Methods—Participants were from the Uganda AIDS Rural Treatment Outcomes study and were followed quarterly for blood draws and structured interviews. We measured food insecurity with the validated Household Food Insecurity Access Scale. Our primary outcomes were: 1) Antiretroviral therapy (ART) non-adherence (adherence<90%) measured by visual analog scale; 2) incomplete viral load suppression (>400 copies/ml); and 3) low CD4 cell count (<350 cells/mm^3). We used generalized estimating equations to estimate the associations, adjusting for socio-demographic and clinical variables.

Results—We followed 438 participants for a median of 33 months; 78.5% were food insecure at baseline. In adjusted analyses, food insecurity was associated with higher odds of ART non-adherence [Adjusted Odds Ratio [AOR]=1.56, 95% confidence interval [CI]=1.10–2.20; p<0.05],

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incomplete viral suppression [AOR= 1.52, 95% CI 1.18–1.96; p<0.01], and CD4 cell count <350 [AOR=1.47, 95% CI 1.24–1.74; p<0.01]. Adding adherence as a covariate to the latter two models removed the association between food insecurity and viral suppression, but not between food insecurity and CD4 cell count.

Conclusions—Food insecurity is longitudinally associated with poor HIV outcomes in rural Uganda. Intervention research is needed to determine the extent to which improved food security is causally related to improved HIV outcomes and to identify the most effective policies and programs to improve food security and health.

Introduction

Food insecurity, defined as having insufficient access to safe, nutritionally adequate foods or needing to acquire foods in social unacceptable ways [1], is common in resource –poor settings, particularly among HIV-infected populations[2, 3]. Food insecurity contributes to worse health-related quality of life [4], depression [5, 6], increased hospitalizations [4, 7], and higher morbidity [4, 7] among HIV-infected individuals. Cross sectional and qualitative studies suggest that food insecurity may negatively impact antiretroviral treatment (ART) response [8, 9], thereby jeopardizing the success of new ART programs. As a result, improving food security may be an effective way to support HIV treatment adherence and retention in care [10, 11], and international organizations have begun to integrate food, nutrition and HIV/AIDS care initiatives [12–15]. Effective programming requires robust data from well-designed studies to determine the association between, and mechanisms linking, food insecurity and HIV outcomes in order to develop and differentiate between potential interventions.

We examined the longitudinal associations between food insecurity and HIV treatment response in a cohort of HIV-infected individuals receiving ART in rural Uganda. We hypothesized that food insecurity is associated with worse ART adherence, and poorer virologic and immunologic outcomes, and that the association between food insecurity and biologic treatment outcomes is explained by ART non-adherence. [16].

Methods

Participants and Study Design

Participants were from the Uganda AIDS Rural Treatment Outcomes (UARTO) study, a prospective cohort initiated in July 2005 in Mbarara town (population 65,000) within the rural Mbarara District in southwestern Uganda. Patients were eligible if they were initiating ART, were 18 years or older, and lived within 20 km of the Mbarara Immune Suppression Syndrome Clinic. All UARTO participants from August 2007 were enrolled into a sub-study examining the impact of food insecurity on HIV health outcomes and followed until July 2010. We conducted quarterly assessments using standardized instruments administered in Runyankole by a native speaker and performed phlebotomy for plasma HIV RNA levels and CD4+ T cell count. Informed consent was obtained from all participants. We obtained ethical approval from institutional review boards at the University of California at San Francisco, Partners Healthcare, and Mbarara University of Science and Technology.

Measures

We measured food insecurity, the primary explanatory variable, with the Household Food Insecurity Access Scale (HFIAS), a nine-item scale based on validation studies in 8 countries [17–19]. Cronbach's alpha in the baseline sample was 0.91. A dichotomous variable for being food secure versus food insecure was created from a standard algorithm [17].

Primary outcomes—(1) ART non-adherence: ART adherence was measured quarterly using the visual analog scale (VAS) [20, 21]. Participants marked the amount of each antiretroviral drug taken over the previous 7 days, on a scale ranging from 0–100% [22, 23]. ART non-adherence was defined as <90% adherence (compared to ≥90% adherence), averaging across all drugs in the patient's regimen, based on previous literature showing that adherence <90% is associated with increased progression to AIDS [24, 25]. (2) Incomplete viral load suppression was defined as HIV-1 viral load > 400 copies/ml. HIV-1 viral load determinations were made at the Mulago University-Johns Hopkins University (MUJHU) Laboratory in Kampala using the Roche Cobas Amplicor HIV 1 Monitor version 1.5 with a lower limit of quantification of 400 copies/ml. (3) Low CD4 cell count (also processed at MUJHU) was defined as CD4 cell count <350 cells/mm^3, the threshold for ART initiation recommended by the World Health Organization [26] and associated with greater survival on ART [27] (dichotomous).

We selected covariates based on prior literature and our conceptual framework showing hypothesized links between food insecurity and HIV health outcomes [16]. Baseline sociodemographic and clinical covariates included: age, sex, marital status, education, ART status at baseline, and pre-ART CD4 cell count measured in 100 cell increments. Time-varying variables included employment, household asset index [28], positive screen for heavy drinking as measured by the 3-item consumption subset of the Alcohol Use Disorders Identification Test (AUDIT-C) [29], and tobacco use in the past thirty days.

Analysis

We used generalized estimating equations (GEE) to separately model the marginal expectation of the primary outcomes as a function of food insecurity and time. All analyses were conducted using PROC GLMMIX in SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina). For each outcome, covariates with a $p \leq 0.2$ in bivariate analysis were included in adjusted models. To evaluate the hypothesis that ART adherence is a potential mechanism through which food insecurity is adversely associated with virologic and immunologic outcomes, we added time-varying ART adherence to the adjusted models for incomplete viral load suppression, and added both ART adherence and viral load suppression to the adjusted models for low CD4 cell count. We then reassessed the magnitude and statistical significance of the estimates of the relationship between food insecurity and these two outcomes.

We implemented sensitivity analyses to test the robustness of our results to alternate model specifications, including using categorical food insecurity (mild, moderate and severe food insecurity versus food secure) as our primary explanatory variable, introducing a 3-month

lag for the explanatory variables, and including duration of ART as a covariate in models restricted to those on ART for at least one year duration.

Results

The study included 438 participants followed for a median of 33.0 months (IQR=21.9–35.7). The majority (99%) were on non-nucleoside reverse transcriptase inhibitor-based regimens throughout the study, and the proportion on one-pill fixed-dose combination ART increased from 7.3% in 2007 to 22.1% in 2010. At baseline, 78% of participants were food insecure (Table S1). Half of these – or 39% of all participants – were severely food insecure. Median pre ART CD4 count was 137 cells/mm^3 and median pre-ART VL was 109,615 copies/ml. During follow-up, 28.6% of all participants reported adherence under 90% during at least one visit and 63.9% of participants had incomplete viral suppression during at least one visit.

Associations between food insecurity and HIV-related outcomes

Food insecurity was associated with 67% higher odds of ART non-adherence in unadjusted models, and 56% greater odds of ART non-adherence in adjusted models (AOR=1.56; 95% CI 1.10–2.20; p<0.01; Table 1). Evaluated at the mean of other covariates averaged over the course of follow-up, 7.0% of those with any food insecurity were non-adherent compared with 4.6% of those with no food insecurity, a 52% relative difference. Food insecurity was also associated with 30% higher odds of incomplete viral suppression in unadjusted analyses, and with 52% higher odds of incomplete viral suppression in adjusted analyses (AOR=1.52; 95% CI 1.18–1.96; p<0.01; Table 1). Evaluated at the mean of other covariates averaged over the course of follow-up, 11.0% of those with any food insecurity were not suppressed compared with 7.5% of those with no food insecurity, a 47% relative difference.

Food insecurity was associated with 22% higher odds of having a CD4 count less than 350 cells/mm^3 in unadjusted analyses, and 47% greater odds of low CD4 cell count in adjusted analyses (AOR=1.47, 95% CI 1.24–1.74; p<0.001; Table 2). Of those with any food insecurity, 69.9% had CD4<350 during follow-up versus 61.3% of those with no food insecurity, a 13% relative difference.

Adjusting for adherence as a potential pathway variable

In regression models of virologic suppression including ART adherence, adherence <90% was associated with over two times higher odds of incomplete viral suppression, and food insecurity was no longer significantly associated with incomplete viral suppression (AOR=0.96; 95% CI 0.68–1.35; p=0.80; Table 1). In adjusted models for low CD4 cell count including time-varying ART adherence and viral load suppression at CD4 determination, ART adherence < 90% was associated with 58% higher odds of CD4 count < 350. The association between food insecurity and low CD4 count retained statistical significance (AOR=1.47; 95% 1.21–1.77; p<0.001; Table 2). Sensitivity analyses did not significantly alter the main results (Table S2).

Discussion

In this longitudinal study in rural Uganda, food insecurity was common and associated with poor ART adherence and worse biologic treatment outcomes. Low ART adherence was an important mechanism through which food insecurity appeared to negatively influence virologic outcomes. While intervention studies are needed to confirm that improved food security is causally connected with improved HIV treatment outcomes, these findings provide further support that alleviating food insecurity may improve biologic treatment response and thereby reduce morbidity and mortality among HIV-infected populations.

Our work is consistent with qualitative and cross-sectional studies showing that food insecurity is associated with ART non-adherence, incomplete viral load suppression and low CD4 cell counts [9, 30–33]. While ART adherence was an important mediator of virologic outcomes, consistent with our previously published conceptual framework [16], this was not the case for CD4 cell counts. This may be because CD4 cell responses also relate to nutritional pathways and to pre-treatment CD4 cell counts, which may be negatively affected by food insecurity if food insecure individuals present late to care [34].

Responding to the evidence of adverse impacts of food insecurity on the HIV/AIDS epidemic, international organizations have called for the implementation of food and nutrition support and counseling as part of the essential HIV/AIDS package [12, 35]. A few small intervention studies have demonstrated that food supplementation at the clinic can lead to improved ART adherence, food security, body mass index and clinic attendance, [36–38], but these need to be confirmed in larger studies measuring treatment responses. To address food insecurity and its negative consequences including poor ART adherence, broader interventions beyond short-term food supplementation should be considered to address upstream drivers of food insecurity and all of the pathways through which food insecurity negatively affects health. Global institutions such as WHO [39], UNAIDS [40], World Bank [41], American Dietetic Association [42], and the International Fund for Agricultural Development [43], have begun to shift attention to longer-range food security strategies such as livelihood enhancement [44–46]. Studies are needed to evaluate the impacts of different types of food security interventions on immunologic and virologic outcomes, in specific contexts and of varying duration [35], to better understand which mitigation strategies are most acceptable and cost-effective in specific contexts.

Although we used a self-reported measure of ART adherence, which may incompletely capture the variance in adherence behavior, VAS was strongly associated with both incomplete viral suppression and low CD4 counts, thereby supporting its construct validity. Participants in our study had very good ART adherence and virologic responses, which may limit generalizability to other populations. It is possible that food insecurity is a consequence rather than a cause of worse HIV treatment health outcomes. Yet, the finding that food insecurity contributed to worse immunologic outcomes even in lagged-covariate models, coupled with evidence from other studies[47], suggests that food insecurity may be causally related to poor outcomes. Intervention studies will be needed to fully understand the extent to which improved food security is causally related to better HIV treatment responses, and to

determine which aspects of food insecurity are most important to address to improve HIV treatment outcomes.

In summary, we found that food insecurity is highly prevalent among HIV-infected individuals in rural Uganda, and is associated with worse ART adherence and worse virologic and immunologic outcomes. Our study further supports the need to foster integration of resources and systems responding to the parallel epidemics of food insecurity and HIV/AIDS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Factors associated with non-adherence and incomplete viral suppression among ART clients in Uganda

	Adherence < 90%		HIV-1 viral load > 400 copies/ml		
Characteristic	**(1) Unadjusted OR (95% CI)**	**(2) Adjusted OR (95% CI)**	**(3) Unadjusted OR (95% CI)**	**(4) Adjusted OR (95% CI)**	**(5) Adjusted OR (95% CI) with adherence**
Any food insecurity	1.67 (1.23–2.26)***	1.56 (1.10–2.20)*	1.30 (1.04–1.63)*	1.52 (1.18–1.96)**	0.96 (0.68–1.35)
Age (per 10 years)	0.53 (0.44–0.64)***	0.59 (0.48–0.73)***	0.66 (0.58–0.75)***	0.66 (0.58–0.77)***	0.63 (0.51–0.79)***
Male (vs female)	0.67 (0.49–0.90)**	0.83 (0.57–1.19)	1.28 (1.05–1.57)*	1.54 (1.19–1.99)***	2.54 (1.77–3.63)***
Less than high school education	0.96 (0.72–1.29)		1.28 (1.01–1.61)*	1.31 (0.99–1.72)	2.03 (1.30–3.16)**
Employed	0.58 (0.45–0.76)***	0.70 (0.52–0.95)*	0.93 (0.76–1.15)		
Asset index ≠ (continuous)	0.92 (0.85–0.99)*	0.97 (0.89–1.05)	0.95 (0.90–1.00)	1.02 (0.96–1.08)	1.03 (0.93–1.13)
Married	1.02 (0.79–1.32)		0.79 (0.65–0.96)*	0.77 (0.62–0.96)*	0.58 (0.42–0.81)**
Problem drinking	2.48 (1.45–4.23)***	2.56 (1.41–4.66)**	3.57(2.48–5.15)***	2.51 (1.69–3.72)***	1.10 (0.53–2.28)
Tobacco use, past 30 days	1.09 (0.58–2.04)		1.71 (1.15–2.56)**	1.07 (0.66–1.73)	0.88 (0.42–1.88)
Pre-ARV CD4 (per 100 units)	0.88 (0.76–1.02)	0.90 (0.78–1.05)	0.99 (0.90– 1.10)	0.96 (0.87–1.07)	0.98 (0.84–1.14)
ART naïve at baseline	1.84 (1.42–2.40)***	1.64 (1.23–2.00)***	3.51 (2.84–4.35)***	3.09 (2.46–3.88)***	0.99 (0.73–1.36)
Adherence < 90%			2.08 (1.36–3.20)***		2.22 (1.41–3.48)***

*** p<0.001

** p<0.01

* p<0.05

Note: Columns (1) and (3) show results from an unadjusted models of the bivariate association with adherence and incomplete viral suppression, respectively, and each characteristic. Column (2) shows results from a regression model of food insecurity on adherence adjusting for all factors significant at α=0.2 from column (1). Column (4) shows results from a regression model of food insecurity on incomplete viral suppression adjusting for all factors significant at α=0.2 from column (3). Column (5) adds adherence to the model from column (4) to explore its role as a potential mediator of the relationship between food insecurity and incomplete viral suppression.

≠ Asset index created using 25 variables related to assets following the methodology proposed by Filmer and Pritchett [28]. Higher values indicating greater household wealth

Table 2

Factors associated with CD4 < 350 among ART clients in Uganda

Characteristic	(1) Unadjusted OR (95% CI)	(2) Adjusted OR (95% CI)	(3) Adjusted OR (95% CI) with adherence and VL suppression
Any food insecurity	1.22 (1.05–1.40)**	1.47 (1.24–1.74)***	1.47 (1.21–1.77) ***
Age (per 10 years)	1.03 (0.96–1.12)		
Male (vs female)	1.74 (1.49–2.02)***	1.66 (1.39–1.98)***	1.91 (1.57–2.32)***
Less than high school education	1.30 (1.12–1.51)***	1.46 (1.22–1.76)***	1.39 (1.13–1.71)**
Employed	1.07 (0.92–1.23)		
Asset index ≠(continuous)	0.97 (0.94–1.00)	1.03 (0.99–1.08)	1.04 (0.99–1.10)
Married	1.07 (0.94–1.22)		
Problem drinking	1.75 (1.20–1.79)**	1.60 (1.02–2.49)*	1.45 (0.84–2.49)
Tobacco use, past 30 days	0.92 (0.67–1.26)		
ART naïve at baseline	1.53 (1.34–1.75)***	1.73 (1.48–2.02) ***	1.63 (1.38–1.94) ***
Pre ART cd4 per 100	0.41 (0.38–0.45)***	0.39 (0.36–0.43) ***	0.38 (0.34–0.42)***
VL<400	3.62 (2.77–4.73)***		1.69 (1.15–2.49)**
Adherence < 90%	1.76 (1.31–2.37)***		1.58 (1.11–2.23)*

*** p<0.001

** p<0.01

* p<0.05

Note: Column (1) shows results from an unadjusted model of the bivariate association between CD4<350 and each characteristic. Column (2) shows results from a regression model of food insecurity on CD4<350 adjusting for all factors significant at α=0.2 from column (1). Column (3) adds viral suppression and adherence to the model from column (2) to explore their role as potential mediators of the relationship between food insecurity and CD4<350.

≠Asset index created using 25 variables related to assets following the methodology proposed by Filmer and Pritchett [28]. Higher values indicating greater household wealth