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Food Insecurity and T-cell Dysregulation in Women Living With Human Immunodeficiency Virus on Antiretroviral Therapy

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Background. Food insecurity is associated with increased morbidity and mortality in people with human immunodeficiency virus (HIV) on antiretroviral therapy, but its relationship with immune dysregulation, a hallmark of HIV infection and comorbidity, is unknown.

Methods. In 241 women participating in the Women's Interagency HIV Study, peripheral blood mononuclear cells were characterized by flow cytometry to identify cell subsets, comprising surface markers of activation (%CD38+HLADR+), senescence (%CD57+CD28−), exhaustion (%PD-1+), and co-stimulation (%CD57− CD28+) on CD4+ and CD8+ T cells. Mixed-effects linear regression models were used to assess the relationships of food insecurity with immune outcomes, accounting for repeated measures at ≤3 study visits and adjusting for sociodemographic and clinical factors.

Results. At the baseline study visit, 71% of participants identified as non-Hispanic Black, 75% were virally suppressed, and 43% experienced food insecurity. Food insecurity was associated with increased activation of CD4+ and CD8+ T cells, increased senescence of CD8+ T cells, and decreased co-stimulation of CD4+ and CD8+ T cells (all $P < .05$), adjusting for age, race/ethnicity, income, education, substance use, smoking, HIV viral load, and CD4 count. In stratified analyses, the association of food insecurity with CD4+ T-cell activation was more pronounced in women with uncontrolled HIV (viral load >40 copies/mL and CD4 <500 cells/mm^3) but remained statistically significant in those with controlled HIV.

Conclusions. Food insecurity may contribute to the persistent immune activation and senescence in women with HIV on antiretroviral therapy, independently of HIV control. Reducing food insecurity may be important for decreasing non–AIDS-related disease risk in this population.

Keywords. food insecurity; HIV; immune activation; senescence; exhaustion.

With the ongoing success of antiretroviral therapy (ART), life expectancy for people living with human immunodeficiency virus (HIV) approaches that of the general population [1]. Yet, despite suppression by ART, HIV infection leads to persistent immune dysregulation [2], characterized by elevated markers of T-cell activation, exhaustion, and senescence [3]. This immune dysregulation may contribute to the higher risk of non–HIV-related conditions (eg, cardiovascular disease, neurocognitive decline, cancer) observed in people living with HIV compared with people without HIV [4]. Hypothesized causes of persistent immune dysregulation in treated HIV infection include low-level viral replication, the latent HIV reservoir, microbial translocation, coinfection with other viruses, and lymphoid fibrosis [5].

While clinical research targeting these potential determinants of persistent immune dysregulation is ongoing [5], less attention has been focused on social determinants of immune dysregulation in HIV. People living with HIV, particularly women, disproportionately experience food insecurity, defined as limited or uncertain availability of nutritionally adequate, safe foods and/or the inability to acquire food in socially acceptable ways [6]. Food insecurity is associated with worse adherence to ART [7], poor HIV control [8], and increased morbidity and mortality among people with HIV [9–11]. However, poor adherence to ART may not fully explain the increased mortality risk associated with food insecurity [10], and other mechanisms may play a role.

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We recently reported that food insecurity was related to increased levels of plasma inflammatory markers interleukin 6 (IL-6) and tumor necrosis factor recepter 1 (TNFR1) in HIV-positive women on ART, even among those with well-controlled HIV (ie, virally suppressed and high CD4 count) [12]. Persistent inflammation and immune activation are closely interconnected processes that are both highly prevalent in HIV infection, and both contribute to immune exhaustion and immunosenescence [3]. Persistent T-cell activation, senescence, and exhaustion are each different states of T-cell dysfunction—activation is characterized by high effector function, proliferation, and cytotoxicity; senescence by low proliferative activity, high differentiation, and shortened telomeres [13]; and exhaustion by poor effector function and sustained expression of inhibitory receptors [14]. T-cell co-stimulatory molecules (eg, CD28) are necessary for T-cell activation, proliferation, and survival, and are lost with aging and immunosenescence [15]. In this same population of women with HIV on ART, we aimed here to examine the hypothesis that food insecurity is related to higher levels of immune activation (%CD38+HLADR+), exhaustion (%PD-1+), and senescence (%CD57+CD28−), and lower levels of co-stimulation (%CD57−CD28+), of CD4+ and CD8+ T cells. We further explored whether pathways of HIV control, nutrition, and microbial translocation may explain observed relationships of food insecurity with immune outcomes.

METHODS

Study Population

The Women's Interagency HIV Study (WIHS) is a multisite cohort study of women with HIV and demographically similar women without HIV in the United States that collected clinical, demographic, and behavioral data semiannually through interviews, physical examinations, and laboratory tests [16]. Participants provided informed consent and were compensated for participation.

Beginning in 2013, the Food Insecurity Substudy added measures of food security and dietary intake to WIHS interviews. The present study includes 241 participants with HIV on ART who were enrolled in the substudy from 5 sites (Bronx, New York; Brooklyn, New York; Washington, DC; San Francisco, California; Chicago, Illinois) and had available T-cell data for at least 1 visit, as well as food security and covariate data at the visit; participants with cancer, autoimmune disease, or hepatitis B or C virus infection were excluded from analyses. Data were collected annually from April 2013 through September 2015, and participants provided a total of 616 person-visits with complete outcome, exposure, and covariate data.

This research was approved by the Institutional Review Boards of all the WIHS sites, and conducted in accordance with the Declaration of Helsinki.

Laboratory Methods

Immune phenotyping was performed from 2016 to 2018 by multiparameter flow cytometry on frozen/thawed peripheral blood mononuclear cells (PBMCs). PBMCs were removed from LN_2 storage and thawed rapidly in a 37°C water bath, washed, and stained with fluorochrome-conjugated monoclonal antibodies to CD3, CD4, CD8, CD57, CD28, PD-1, HLADR, and CD38 (BD Biosciences). To assess viability, PBMCs were stained with an Aqua Live/Dead cell stain kit (Invitrogen) prior to cell surface staining. After staining, cells were washed, fixed in 2% formaldehyde, and analyzed within 24 hours on an LSRII flow cytometer (BD) using FACS Diva software v6.11. Data analysis was performed using FlowJo 9.9.3 (Tree Star, Inc). Analyses of immune activation (CD38+HLADR+), exhaustion (PD-1+), senescence (CD57+CD28−), and co-stimulation (CD57−CD28+) were performed after stringent gating on singlet live ($Aqua^-$) CD3+CD4+ or CD3+CD8+ T cells.

The following biomarkers of microbial translocation were measured on frozen/thawed plasma by enzyme-linked immunosorbent assay according to the manufacturers' instructions: intestinal fatty acid binding protein (IFAB), soluble CD14 (sCD14), and soluble CD163 (sCD163) (R&D Systems).

Study Measures

The outcome variables were cell surface markers of activation (%CD38+HLADR+), senescence (%CD57+CD28−), exhaustion (%PD-1+), and co-stimulation (%CD57− CD28+) on CD4+ and CD8+ T cells. To facilitate comparison between outcomes in statistical analyses, these variables were *z*-score standardized.

The exposure was household food insecurity over the past 6 months, assessed using the validated 18-item US Department of Agriculture Household Food Security Survey Module (HFSSM) [17], which measures uncertainty about food supplies, insufficient diet quality, and insufficient food quantity. For households with 1 or more child, raw scores for high, marginal, low, and very low food security are 0, 1–2, 3–7, and 8–18, respectively [17]. For households with no children, raw scores for high, marginal, low, and very low food security are 0, 1–2, 3–5, and 6–10, respectively [17]. A binary variable was created to capture any food insecurity (marginal, low, or very low food security), hereafter referred to as "food insecurity," compared with no food insecurity, hereafter referred to as "food security." Cronbach's α for the HFSSM in this sample was high (α = 0.88), indicating high internal consistency.

A priori control variables for model adjustment were selected based on factors consistently related to food insecurity in prior research [18]. These were age at visit (years), average annual household income (<$12 000, $12 001–$24 000, or ≥$24 001), race/ethnicity (non-Hispanic White, Hispanic, non-Hispanic Black/African American, or other), high school education,

illicit substance use since last visit (excluding marijuana), and current cigarette smoking.

We considered other variables potentially involved in the relationship of food insecurity with immune markers for model adjustment. These were HIV-related clinical factors (viral load [< or ≥40 copies/mL] and CD4 count [< or ≥500 cells/mm^3]), body mass index (BMI; kg/m^2), nutritional variables (dietary intake of fat, sugar, red and processed meat, and fruits and vegetables; servings/day), and indirect markers of microbial translocation (IFAB [pg/mL], sCD14 [ng/mL], and sCD163 [ng/mL]). Dietary intake was assessed using an adapted version of the 2000 National Health Interview Survey multifactor screener [19]. The HIV clinical variables were included in fully adjusted models based on prior knowledge of their relationship with food insecurity [9] and immune dysregulation [20]. Criteria for inclusion of other variables in multivariable regression were association with food insecurity ($P < .10$) and with any immune markers ($P < .10$).

Statistical Analysis

The stability of immune markers and food security score over the visits was assessed using intraclass correlation coefficients (ICCs), with ICC values less than 0.5, 0.50–0.75, 0.75–0.90, and greater than 0.90 indicating poor, moderate, good, and excellent consistency, respectively [21]. Correlations between markers at each visit were assessed using the Pearson correlation coefficient. Immune outcomes were modeled using mixed-effects linear regression via the Stata "xtreg" command, which uses random effects with a general least-squared estimator to produce a matrix-weighted average of between- and within-person results. We examined associations of each control variable with the immune outcomes in bivariate (ie, unadjusted) mixed-effects linear regressions. Associations of food insecurity with the immune outcomes were also examined using mixed-effects linear regression in unadjusted, minimally adjusted (for a priori control variables), and fully adjusted (for a priori control variables, HIV clinical variables, and other potential mediators) models. As an additional sensitivity analysis, we stratified by HIV control, defined as undetectable viral load (viral load <40 copies/mL) and CD4 count of 500 cells/mm^3 or greater; stratification was conducted at the level of the person-visit. A P value of less than .05 was considered nominally statistically significant; a false discovery rate q-value less than 0.05 was considered statistically significant after adjustment for multiple comparisons. All analyses were conducted in Stata version 14 (StataCorp, 2014; College Station, TX).

RESULTS

Participant Characteristics

The study population included 103 women (43%) with food insecurity (marginal, low, or very low food security) and 138 women (57%) with food security at the baseline substudy visit. Women in this study tended to be middle-aged (median [interquartile range] = 46 [40–50] years), and the majority identified as non-Hispanic Black (71%) and were virally suppressed (75%). The food security score was moderately consistent over the 3 visits (ICC, .56; 95% confidence interval, .48–.63). Women who experienced food insecurity had lower income, were more likely to currently smoke, and consumed diets higher in fat and sugar, compared with women with food security (Table 1).

Attributes of the T-cell Immune Outcomes

The immune markers showed variable consistency over the 3 visits, with markers of senescence showing the highest consistency, followed by markers of exhaustion, activation, and co-stimulation (Figure 1A, Supplementary Table 1). As expected, there were strong positive correlations between immune markers of the same class on CD4+ and CD8+ T cells, as well as between markers of activation and exhaustion, and negative correlations between markers of senescence and co-stimulation (Figure 1B). Many participant characteristics were related to immune marker levels in unadjusted bivariate analysis (Supplementary Table 2). For example, Black and Hispanic women had greater activation and senescence of CD8+ T cells, and greater exhaustion of CD4+ T cells, compared with non-Hispanic White women. Additionally, women with detectable HIV viral load or low CD4 cell count had increased activation and exhaustion of CD4+ and CD8+ T cells (Supplementary Table 2).

Associations of Food Insecurity With T-cell Immune Outcomes

Food insecurity was significantly associated with increased activation of CD4+ and CD8+ T cells, increased senescence of CD8+ T cells, increased exhaustion of CD4+ T cells, and decreased co-stimulation of CD4+ and CD8+ T cells, after adjusting for age, race/ethnicity, income, education, illicit substance use, and smoking (all $P < .05$) (Table 2, Figure 2). Food insecurity was also associated with increased senescence of CD4+ T cells and increased exhaustion of CD8+ T cells; however, these associations did not reach statistical significance. Upon further adjustment for HIV viral load and CD4 cell count, we observed some attenuation of the effect of food insecurity on activation of CD4+ and CD8+ T cells, primarily due to CD4 cell count adjustment, although associations remained statistically significant (Table 2, Figure 2). Further adjustment for HIV viral load and CD4 cell count also attenuated effects of food insecurity on CD4+ T-cell exhaustion, such that the association was no longer significant, again primarily due to CD4 count adjustment. Further adjustment for nutritional variables did not change model estimates (Supplementary Table 3); we did not adjust for BMI and indicators of microbial translocation due to a lack of association with food insecurity and/or the immune outcomes.

Table 1. Characteristics of the Study Participants by Food Insecurity Status

Characteristic	All (N = 241)	Food Security (n = 138)	Food Insecurity (n = 103)
Age, median (IQR), years	46.0 (40.0, 50.0)	47.0 (40.0, 52.0)	46.0 (41.0, 49.0)
Race/ethnicity, n (%)			
White (non-Hispanic)	25 (10.4)	18 (13.0)	7 (6.8)
Hispanic	33 (13.7)	14 (10.1)	19 (18.4)
Black/African American (non-Hispanic)	172 (71.4)	99 (71.7)	73 (70.9)
Other	11 (4.6)	7 (5.1)	4 (3.9)
Annual household income, n (%)			
<$12 000	100 (42.2)	49 (36.6)	51 (49.5)
$12 001–$24 000	51 (21.5)	24 (17.9)	27 (26.2)
≥$24 001	86 (36.3)	61 (45.5)	25 (24.3)
High school education or more, n (%)	161 (66.8)	99 (71.7)	62 (60.2)
Any illicit substance use since last visit, n (%)	10 (4.2)	4 (2.9)	6 (5.9)
Current smoker,[a] n (%)	71 (29.5)	31 (22.5)	40 (38.8)
Detectable viral load (≥40 copies/mL), n (%)	61 (25.4)	32 (23.2)	29 (28.4)
CD4 <500 cells/mm^3, n (%)	76 (31.7)	38 (27.7)	38 (36.9)
BMI, median (IQR), kg/m^2	29.9 (25.6, 35.4)	29.5 (25.4, 34.6)	30.9 (26.2, 37.5)
Intake of high-fat foods,[b] median (IQR), servings	1.6 (1.0, 2.7)	1.5 (0.9, 2.3)	2.2 (1.2, 3.6)
Intake of sugar,[b] median (IQR), servings	1.1 (0.4, 1.9)	0.9 (0.3, 1.6)	1.3 (0.7, 2.1)
Intake of red and processed meats, median (IQR), servings	3.1 (2.2, 4.3)	3.0 (2.0, 4.1)	3.5 (2.3, 4.7)
Intake of fruit and vegetables, median (IQR), servings	1.4 (1.0, 2.0)	1.4 (1.0, 2.0)	1.3 (0.8, 2.0)
sCD14, median (IQR), ng/mL	1485.3 (1132.5, 1911.3)	1481.4 (1132.5, 1994.3)	1486.5 (1113.9, 1887.1)
sCD163, median (IQR), ng/mL	488.9 (361.4, 666.7)	467.1 (361.3, 660.4)	506.8 (361.4, 722.2)
IFAB, median (IQR), pg/mL	1125.9 (705.1, 1717.9)	1081.1 (759.1, 1679.3)	1151.7 (656.0, 1745.9)

Data are presented for the first visit with food insecurity data. Abbreviations: BMI, body mass index; IFAB, intestinal fatty acid binding protein; IQR, interquartile range; sCD14, soluble CD14; sCD163, soluble CD163.

[a] $P < .05$ for difference between food security and food insecurity, Pearson's chi-square test.
[b] $P < .05$ for difference between food security and food insecurity, Wilcoxon rank-sum test.

In fully adjusted models, the association of food insecurity with immune outcomes (activation of CD4+ and CD8+ T cells, senescence of CD8+ T cells, and co-stimulation of CD4+ and CD8+ T cells) tended to be lower in magnitude than those of viral suppression and CD4 cell count, but higher in magnitude than risk behaviors such as illicit substance use and current smoking, with some exceptions (Supplementary Table 4). For example, the association of food insecurity with CD4+ T-cell activation was 75% and 30% of the magnitude of viral suppression and low CD4 cell count, respectively, and 53% higher

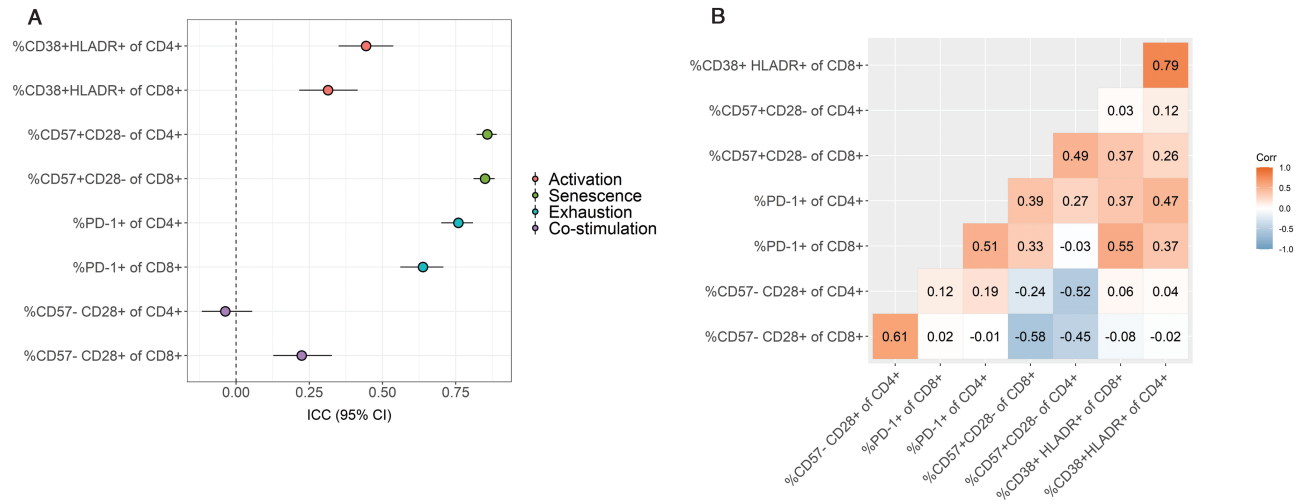

Figure 1. Within- and between-subject correlations of T-cell immune outcomes. *A*, ICCs of the immune markers across 3 years, with up to 3 visits per subject. *B*, Pearson's correlations between the immune markers at the baseline study visit. Correlations were similar at the other 2 visits. Abbreviations: Corr, correlation; ICC, intraclass correlation coefficient.

Table 2. Associations of Food Insecurity With T-cell Activation (%CD38+HLADR+), Senescence (%CD57+CD28–), Exhaustion (%PD-1+), and Co-stimulation (%CD57–CD28+)

	Unadjusted			Minimally Adjusted[a]			Fully adjusted[b]		
Outcome	β (95% CI)	*P*	*q*-Value	β (95% CI)	*P*	*q*-Value	β (95% CI)	*P*	*q*-Value
%CD38+HLADR+ of CD4+	.33 (.17, .49)	<.01	<0.01	.32 (.16, .48)	<.01	<0.01	.26 (.10, .42)	<.01	<0.01
%CD38+HLADR+ of CD8+	.28 (.10, .46)	<.01	<0.01	.25 (.07, .43)	<.01	<0.01	.19 (.03, .35)	.02	0.03
%CD57+CD28– of CD4+	.09 (–.01, .19)	.08	0.09	.09 (–.01, .19)	.07	0.08	.09 (–.01, .19)	.08	0.11
%CD57+CD28– of CD8+	.17 (.07, .27)	<.01	<0.01	.17 (.07, .27)	<.01	<0.01	.15 (.05, .25)	<.01	<0.01
%PD-1+ of CD4+	.13 (.01, .25)	.03	0.04	.13 (.01, .25)	.04	0.05	.10 (–.02, .22)	.10	0.12
%PD-1+ of CD8+	.09 (–.05, .23)	.23	0.23	.08 (–.06, .22)	.31	0.31	.04 (–.1, .18)	.56	0.56
%CD57–CD28+ of CD4+	–.27 (–.45, –.09)	<.01	<0.01	–.34 (–.54, –.14)	<.01	<0.01	–.32 (–.52, –.12)	<.01	<0.01
%CD57–CD28+ of CD8+	–.21 (–.39, –.03)	.01	0.02	–.33 (–.51, –.15)	<.01	<0.01	–.29 (–.47, –.11)	<.01	<0.01

N = 241; person-visits = 616. Results are from mixed-effects linear regression with food insecurity (food insecurity vs food security as reference) as the predictor and *z*-score–standardized immune marker outcomes. Units of the B-coefficient are the difference in standard deviations of the outcome for food insecurity vs food security. Abbreviation: CI, confidence interval.

[a]Models are adjusted for age at visit (years), average annual household income (<$12 000, $12 001–$24 000, or ≥$24 001), race/ethnicity (non-Hispanic White, Hispanic, Black/African American, or other), high school education, illicit substance use since last visit, and current smoking.

[b]Models are adjusted for all variables in the minimally adjusted models, as well as viral load (< or ≥40 copies/mL) and CD4 count (< or ≥500 cells/mm^3).

than the association of current smoking. When evaluating dose-response using 4 categories of food security (high, marginal, low, and very low), we observed a significant trend for the outcomes of CD4+ and CD8+ T-cell activation, CD8+ T-cell senescence, and CD4+ and CD8+ T-cell co-stimulation (*P*-trend < .05) (Supplementary Table 5). However, the trend was nonmonotonic for immune activation, with the largest association in the "low" food security category.

To explore whether associations of food insecurity with immune outcomes persist even with well-controlled HIV, we next stratified analyses based on HIV control (Table 3). The association of food insecurity with activation of CD4+ T cells was significantly modified by HIV control (*P*-interaction = .02), while evidence for modification was also observed for the association of food insecurity with CD4+ T-cell exhaustion (*P*-interaction = .06). In the case of CD4+ T-cell activation, the association with food insecurity was stronger among those with uncontrolled HIV, although still statistically significant among those with well-controlled HIV. A similar pattern was observed for CD4+ T-cell exhaustion; however, the association was not statistically significant among those with well-controlled HIV. These patterns were also consistent across analyses stratified by HIV viral load alone or CD4 count alone (data not shown).

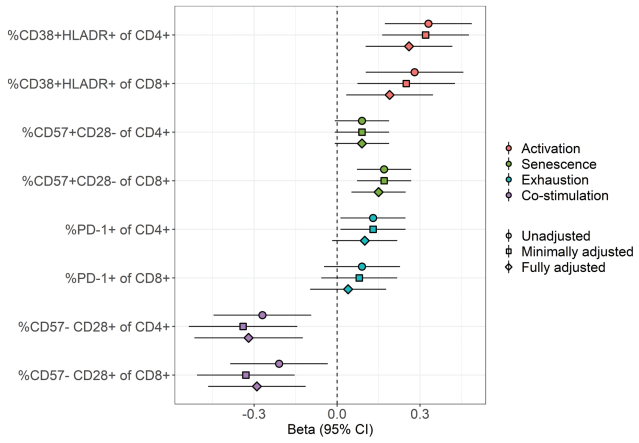

Figure 2. Food insecurity and T-cell immune outcomes. Results of mixed-effects linear regression with food insecurity (food insecurity vs food security) as a predictor of *z*-score–standardized immune marker outcomes. Units of the B-coefficient is the difference in standard deviations of the outcome for food insecurity versus food security. The minimally adjusted model is adjusted for age at visit (years), average annual household income (<$12 000, $12 001–$24 000, or ≥$24 001), race/ethnicity (non-Hispanic White, Hispanic, Black/African American, or other), high school education, illicit substance use since last visit, and current smoking. The fully adjusted model is further adjusted for viral load (< or ≥40 copies/mL) and CD4 count (< or ≥500 cells/mm^3).

DISCUSSION

In this study of women living with HIV on ART, we observed that women experiencing food insecurity had markedly higher levels of immune activation on CD4+ and CD8+ T cells than women with food security, even among those with well-controlled HIV. This suggests that food insecurity may be a key, previously unexplored factor related to persistent immune activation in people living with HIV [2]. We also found that food insecurity was associated with higher senescence of CD8+ T cells, higher exhaustion of CD4+ T cells, and lower co-stimulation of CD4+ and CD8+ T cells, further suggesting a role of food insecurity in immune dysregulation in HIV. Our observation of meaningful effect sizes in relation to other risk factors, and significant trends of worsening immune outcomes with higher food insecurity, lends support to the possibility of a causal relationship. Food insecurity disproportionately affects people with HIV, and women with HIV in particular; in this context, reducing food disparities may be an important means of reducing non–AIDS-related morbidity and mortality in this population.

The observed relationships between food insecurity and immune outcomes may contribute to the high prevalence of adverse

Table 3. Associations of Food Insecurity With T-cell Activation (%CD38+HLADR+), Senescence (%CD57+CD28–), Exhaustion (%PD-1+), and Co-stimulation (%CD57–CD28+), Stratified by HIV Control

	Controlled HIV (n = 178; Person-Visits = 365)		Uncontrolled HIV (n = 142; Person-Visits = 251)	
Outcome	β (95% CI)	*P*	β (95% CI)	*P*
%CD38+HLADR+ of CD4+[a]	.14 (.04, .24)	.01	.56 (.21, .91)	<.01
%CD38+HLADR+ of CD8+	.21 (.03, .39)	.01	.22 (−.09, .53)	.16
%CD57+CD28− of CD4+	.06 (−.06, .18)	.38	.13 (−.07, .33)	.17
%CD57+CD28− of CD8+	.19 (.05, .33)	.01	.20 (.00, .40)	.04
%PD-1+ of CD4+[b]	.03 (−.09, .15)	.60	.28 (.04, .52)	.02
%PD-1+ of CD8+	.10 (−.06, .26)	.26	−.05 (−.32, .22)	.74
%CD57−CD28+ of CD4+	−.33 (−.58, −.08)	.01	−.35 (−.62, −.08)	.02
%CD57−CD28+ of CD8+	−.37 (−.62, −.12)	<.01	−.28 (−.53, −.03)	.03

Results are from mixed-effects linear regression with food insecurity (food insecurity vs food security as reference) as the predictor and *z*-score–standardized immune marker outcomes; HIV control was defined as virally suppressed (<40 copies/mL) and CD4 ≥500 cells/mm^3; all models are adjusted for age at visit (years), average annual household income (<$12 000, $12 001–$24 000, or ≥$24 001), race/ethnicity (non-Hispanic White, Hispanic, Black/African American, or other), high school education, illicit substance use since last visit, and current smoking. Units of the B-coefficient are the difference in standard deviations of the outcome for food insecurity vs food security. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus.

[a] *P*-interaction of food insecurity and HIV control = .02.

[b] *P*-interaction = .06.

clinical outcomes among people with HIV, despite use of ART. T-cell activation is a predictor of mortality in ART-treated HIV [22], is associated with increased cardiovascular disease risk [23], and may increase the risk of other diseases such as cancer [24] and cognitive impairment [25]. The relationship of T-cell senescence, exhaustion, and co-stimulation with non-AIDS morbidity and mortality is less clear, although research suggests that senescence is associated with increased cardiovascular risk [23], exhaustion with failure of immune reconstitution in ART-treated HIV [26], and co-stimulation with resistance of T cells to HIV infection [27]. Taken together, the observed associations of food insecurity with immune parameters may have serious implications for the health of ART-treated women with HIV.

Food insecurity may influence T-cell immune outcomes among people with HIV via several hypothesized mechanisms, including ART adherence and nutritional pathways. Food insecurity is often associated with suboptimal ART adherence in people with HIV [7], resulting in incomplete viral suppression [8] and low CD4 count [28]. Effects of food insecurity on HIV control may, in part, explain the relationship of food insecurity with immune dysregulation, as poor HIV control (and low CD4 count in particular) is a known predictor of immune dysregulation [20]. In line with this, we found that adjusting for CD4 cell count attenuated associations of food insecurity with activation of CD4+ and CD8+ T cells, and exhaustion of CD4+ T cells, suggesting these associations may be explained in part by ART adherence. Yet, associations of food insecurity on T-cell activation are significant upon adjustment for HIV control, and among those with well-controlled HIV in stratified analysis, indicating that pathways independent of ART adherence also contribute to the link between food insecurity and immune activation.

Food insecurity may also influence immune outcomes via nutritional pathways. Individuals with food insecurity often experience malnutrition in the form of inadequate intake of specific foods and nutrients [18]—resulting from the tendency to consume inexpensive energy-dense, nutritionally poor foods [29]—and are at higher risk of obesity [11, 30]. Nutrients [31] and adipose tissue [32] have a wide range of effects on immunity, and nutrition and diet are determinants of the gut microbiome [33] and gut barrier function [34], which also play immune-modulating roles [35–37]. In our study, food insecurity was related to higher intakes of high-fat foods and sugar; however, dietary adjustment did not alter associations of food insecurity with immune outcomes. Additionally, BMI and markers of microbial translocation were not associated with food insecurity in this study population. Yet, we cannot preclude these potential causal pathways, as there are limitations in our measures of nutrition and microbial translocation. The dietary assessment used here does not capture energy intake or micronutrients. BMI does not capture body composition or micronutrient deficiencies. IFAB may be a poor indicator of microbial translocation in high-fat-diet–induced obesity [38], while sCD14 and sCD163 are nonspecific markers of monocyte and macrophage activation. Future research should explore nutritional pathways for food insecurity using more direct measures of nutrition (eg, 24-hour dietary recalls, serum micronutrients, metabolomics), bacterial dysbiosis (eg, stool DNA sequencing), and microbial translocation (eg, serum lipopolysaccharide).

This study was strengthened by the large sample size, availability of multiple T-cell immune outcomes, and longitudinal design, which increased power. The well-characterized WIHS cohort and comprehensive assessment of food insecurity provided an idealized setting to examine associations of

food insecurity with immune outcomes while controlling for confounders and exploring mediational pathways.

Our study also had several limitations. As noted above, direct measurement of nutrition indices and microbial translocation warrants further investigation. Additionally, findings in US women with HIV may not be generalizable to other populations.

In conclusion, we have reported, for the first time, associations between food insecurity and detrimental T-cell immune outcomes in women living with HIV on ART. Effects of food insecurity on immune activation may contribute to previously observed associations of food insecurity with mortality in HIV [10]. While there is an obvious need for effective policy and program interventions to address the widespread food insecurity in women living with HIV, further research to delineate mechanisms by which food insecurity leads to immune dysregulation, independently of ART adherence, may help tailor future solutions to this complex problem. For example, interventions may involve specific dietary, nutrient, or microbial targets (eg, with probiotics) based on identified mechanisms. Improvements in food security in women with HIV may improve T-cell immune phenotypes, and ultimately reduce the risk of non–AIDS-related morbidity and mortality.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. Data in this manuscript were collected by the Women's Interagency HIV Study (WIHS), now the Multicenter AIDS Cohort Study (MACS)/WIHS Combined Cohort Study (MWCCS).

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