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Immune Activation: A Link Between Food Insecurity and Chronic Disease in People Living With Human Immunodeficiency Virus

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Persistent immune activation is a hallmark of human immunodeficiency virus (HIV) infection and thought to play a role on chronic diseases in people with HIV (PWH). Food insecurity is disproportionately prevalent in PWH and is associated with adverse health outcomes. We determined whether food insecurity was associated with increased plasma levels of soluble CD14, CD27, and CD163 in 323 antiretroviral-treated PWH from the Miami Adult Studies on HIV cohort. Nearly half (42.7%) of participants were food insecure, and 85.5% were virally suppressed (<200 copies/mL). Food insecurity was independently associated with higher levels of soluble CD14 and soluble CD27. Very low food security was associated with increased soluble CD163 levels among those with lower $CD4^+$ cell counts. Food insecurity may promote immune activation in PWH, suggesting a biological link between food insecurity and chronic disease among PWH. Improving financial security and access to high-quality diets could reduce the burden of disease in this highly vulnerable population.

Keywords. food insecurity; HIV; immune activation; inflammation.

Infection with human immunodeficiency virus (HIV) results in chronic immune activation and progressive immunodeficiency [1]. Modern antiretroviral therapy (ART) has been effective at controlling viral replication and improving longevity and quality of life for people with HIV (PWH) [2]. Nonetheless, persistent immune activation and inflammation, even with virologic suppression [3], contribute to high rates of chronic comorbid conditions among PWH [4, 5]. Consequently, non–AIDS-defining illnesses have become the predominant causes of disease and death among PWH in settings where ART is readily available [6]. Moreover, PWH suffer from higher rates of multiple comorbid conditions than the general population [7].

In addition to the immune response to HIV infection, many social and lifestyle factors, such as sedentary lifestyle, poor diet quality, and substance abuse, can contribute to inflammation and chronic diseases in PWH. Food insecurity is a social determinant of health that refers to a lack of dependable access to nutritious foods, resulting in reliance on low-cost foods and poor quality diets [8]. In the United States, approximately 10.5% of the population experienced food insecurity at some point during 2019, with significantly higher rates among minority-headed households and those with incomes <185% of the federal poverty line [9]. Food insecurity also disproportionately affects PWH in both high- and low-resource settings [10] and has been associated with several adverse health outcomes in the general US population [11, 12] and PWH [13]. There are several nutrition-related consequences of HIV infection, including increased metabolic demands and altered gastrointestinal absorptive function. Food insecurity further increases the risk for compromised nutritional status (eg, malnutrition, micronutrient deficiencies) [14].

Studies using data from the National Health and Nutrition Examination Survey have established associations of food insecurity with proinflammatory diets [15] and elevated C-reactive protein (CRP) levels [16, 17]. The Women's Interagency HIV Study has associated food insecurity with elevated levels of proinflammatory cytokines interleukin 6 and tumor necrosis factor receptor 1 [18], as well as T-cell activation (percentage $CD38^+HLADR^+$) in women living with HIV [19]. These studies point to biological mechanisms between food insecurity and chronic disease. However, more studies are needed to investigate the association between food insecurity and immune activation—a precursor to chronic disease—in PWH. Therefore, we aimed to determine whether food insecurity was associated with increased monocyte/macrophage (soluble CD14 and soluble CD163 [sCD14 and sCD163]) and lymphocyte (soluble CD27 [sCD27]) activation in PWH.

METHODS

Data from 325 participants from the Miami Adult Studies on HIV (MASH) cohort were cross-sectionally analyzed for this

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study. Criteria for eligibility in the MASH cohort include age ≥40 years, documented HIV and hepatitis C virus status, and seronegativity for hepatitis B virus. All participants provided written informed consent for participation in the study and release of medical information. The MASH cohort has been followed up every 6 months since 2002. At each study visit, participants complete a survey that assesses HIV and other morbid conditions, psychosocial factors and social determinants of health, and substance abuse. We also obtain anthropometric measurements, vital signs, and fasting blood samples at each visit. Participants who were HIV uninfected, hepatitis C virus infected, or not taking ART were excluded from this analysis. The data used in this study were collected between February 2016 and July 2018. The protocols for the study were approved by the institutional review board at Florida International University.

Primary Outcomes: Biomarkers of Immune Activation

Plasma levels of sCD14, sCD27, and sCD163 were quantified by means of analyte-specific bead-based Luminex Multiplex immunoassays (EMD Millipore). Soluble CD14 (sCD14) is shed by CD14-expressing monocytes after stimulation by lipopolysaccharide (LPS; also known as endotoxin) [20]. Consequently, sCD14 serves as a marker of monocyte activation, as well as an indirect, yet nonspecific marker of microbial translocation [20]. Elevated levels of sCD14 and sCD163 persist during effective suppressive ART and are correlated with HIV disease progression [21]. CD163, also known as the hemoglobin scavenger receptor, is expressed in macrophages in response to inflammation [22]. The functions of CD163 have not been fully elucidated [23], but shedding of sCD163 in plasma has been implicated in chronic inflammatory conditions [22]. Soluble CD27 is secreted by antigen-stimulated T cells, thus considered a direct marker of early-stage T-cell activation. Levels of sCD27 are responsive to ART but remain elevated in HIV infection, are correlated with HIV disease progression, and have been particularly associated with AIDS-associated lymphoma [24, 25].

Food Insecurity

The US Department of Agriculture's Household Food Security Survey (HFSS) was used to assess food insecurity [9]. The 18-item instrument determines food security through questions related to conditions and behaviors that characterize food-insecure households. While the HFSS was designed to measure food insecurity at the household level, it has also been validated to measure food insecurity at the individual level [26]. The HFSS can categorize households into 4 levels of food security or by increasing severity of food insecurity: full, marginal, low, and very low food security. Historically, the Department of Agriculture has classified food security as secure (full or marginal) or insecure (low or very low). However, the demographic characteristics of marginally food-secure households more closely resemble those with low or very low food security than those with full food security [27]. Subsequently, similar to others [13, 18, 19], we defined food insecurity as having marginal, low, or very low food security, whereas participants with full food security were considered food secure.

Diet Recalls

Trained research staff conducted 24-hour dietary recall interviews using the multiple-pass method [28]. Participants were provided with visual aids to improve the accuracy of data. Dietary analysis was conducted using NutriBase Pro software (version 17; Cybersoft). Intakes of total energy, energy from protein, carbohydrates, and fats and grams of saturated fatty acids and fiber were considered potential confounders.

Additional Covariates

Sociodemographic data were self-reported. Because both food insecurity and immune activation are associated with several chronic conditions, we incorporated several covariates as potential confounders for the relationship between food insecurity and immune activation. HIV viral load and $CD4^+$ cell counts were abstracted from medical records. Participants were considered virally suppressed if HIV RNA levels were <200 copies/mL. Height, weight, vital signs, and fasting blood were obtained for all participants. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared and reported in 5-kg/m^2 increments for more clinically relevant interpretation.

Hyperglycemia (fasting plasma glucose level ≥100 mg/dL), hypertriglyceridemia (triglyceride level ≥150 mg/dL), and hypertension (≥130 mm Hg systolic or ≥85 mm Hg diastolic blood pressure) were determined. Liver fibrosis was assessed and defined as fibrosis 4 index score ≥1.45 (calculated based on age, platelet count, and serum liver enzyme levels). Systemic inflammation was measured using high-sensitivity CRP (hs-CRP) levels. Substance use, including use of cocaine, cannabis, and heroin, was self-reported and confirmed with urine toxicology (American Bio Medica). Cigarette smoking was self-reported. Hazardous drinking was assessed with the Alcohol Use Disorders Identification Test (AUDIT), using a cutoff score of 8 [29].

Statistical Analysis

Data analysis for the current study was performed using SAS software, Version 9.4 of the SAS System for Windows (SAS Institute). Data were analyzed for outliers and assumptions of normality. Descriptive statistics were reported as number (percentage) or mean (standard deviation [SD]) (or median [interquartile range] if not normally distributed). Participants were grouped as food secure or food insecure (dichotomous) or by levels of food security (4 levels; multicategorical). Group differences were tested with χ^2 tests, *t* tests, and 1-way analysis of variance; owing to skewed distributions for sCD14, sCD27,

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and sCD163, Wilcoxon rank sum and Kruskal-Wallis tests were performed.

Owing to the direction of the hypotheses (ie, food insecurity is associated with higher levels of immune activation), 1-sided *P* values were reported for Wilcoxon rank sum tests. Spearman correlations were used to determine the relationships between markers of immune activation and levels of food insecurity. To assess the relationship between food insecurity and immune activation, linear regressions were performed using log-transformed values of the primary outcomes. Potential confounders were explored with linear regressions, including sociodemographic characteristics (eg, age, sex, race/ethnicity, income, and household size), HIV viral load and CD4 cell counts, metabolic and comorbid parameters, substance abuse, and dietary intake. Statistical significance was set at an α level of .05 and 2-sided *P* values are reported, unless otherwise specified.

RESULTS

Characteristics

Sample characteristics are shown in Table 1. Of the 323 participants in the study, 185 (57.3%) were food secure, and 138 (42.7%) were food insecure, with 53 (16.4%), 43 (13.3%), and 42 (13.0%) participants reporting marginal, low, and very low food security, respectively. The participants had a mean age (SD) of 53.3 (7.8) years, and were predominantly male (n = 197 [61.0%]) and black non-Hispanic (n = 207 [64.1%]) or white Hispanic (n = 65 [20.1%]). Most households had 1 or 2 members, with a mean annual income of $13 315, and 73.1% (n = 233) fell below the federal poverty level (https://aspe.hhs.gov/2020-poverty-guidelines). Most participants had a maximum educational level of high school or less (n = 226 [70.0%]) and were receiving disability benefits (n = 205 [63.5%]) or unemployed (n = 84 [26.0%]).

Only 47 participants (14.5%) did not have suppressed HIV viral loads. The mean CD4 cell count (SD) was 602 (333)/μL, and only 23 participants (7.1%) had CD4 cell counts <200/μL (indicative of AIDS). The mean (SD) BMI was 29.2 (6.1), with 126 (39.0%) of participants classified as obese, and the mean energy intake was 1967 (1150) kcal. In addition, 79 (24.5%) had hyperglycemia, 99 (30.7%) had elevated triglycerides, and 162 (50.2%) had hypertension.

Associations With Food Insecurity

Very low food security was associated with nonsuppressed HIV viral load ($P = .02$) but not CD4 cell count ($P = .9$) (data not shown). Food insecurity was associated with a higher percentage of total energy intake from fats than food security (mean [SD], 37.3% [10.2%] vs 34.5% [12.3%], respectively; $P = .04$). Neither BMI nor total energy intake differed between the 2 groups. No other significant differences in characteristics were observed between food-secure and food-insecure participants, although trends for lower age and incomes, as well as higher hs-CRP level, hazardous drinking, and use of cannabis were noted among food-insecure participants ($P < .1$).

Distribution of Immune Activation Biomarkers

Table 2 shows the median values for sCD14, sCD27, and sCD163 levels. Compared with food security, food insecurity was associated with higher levels of sCD14 (1-sided $P = .005$) and sCD27 (1-sided $P = .003$) but not sCD163 (1-sided $P = .3$). When examining the markers of immune activation by levels of food insecurity, borderline differences for sCD14 ($P = .05$) and sCD27 ($P = .05$) were noted. The lowest levels of sCD14 and sCD27 were found among participants with full food security. In addition, having a nonsuppressed HIV viral load was associated with higher levels of sCD14 (1-sided $P = .01$), sCD27 (1-sided $P < .0001$), and sCD163 (1-sided $P = .03$). The severity of food insecurity was directly correlated with sCD14 (rho = 0.151; $P = .006$) and sCD27 (rho = 0.154; $P = .005$) but not with sCD163 (rho = 0.039; $P = .5$) levels.

Factors Associated With Immune Activation

We performed univariate linear regressions on log-transformed sCD14, sCD27, and sCD163 levels to determine potential confounders for the relationship between food insecurity and markers of immune activation (Table 3). In addition to food insecurity and HIV viral load, markers of immune activation were associated with older age, race/ethnicity, higher BMI, hypertriglyceridemia, hypertension, higher hs-CRP, and liver fibrosis. Higher $CD4^+$ cell counts were associated with lower sCD27 levels. Trends were observed with cigarette smoking and cocaine use. Dietary intakes of total energy, macronutrients, saturated fatty acids, and fiber were not associated with any of the outcomes.

In multiple regressions (Table 4), food insecurity remained significantly associated with sCD14 and sCD27 levels, after adjustment for confounders. While food insecurity and $CD4^+$ cell counts were not independently associated with sCD163 levels, the severity of food insecurity showed a tendency to moderate the relationship between $CD4^+$ cell counts and sCD163 levels ($F = 2.35$; $P = .07$). Compared with full food security, very low food security was significantly associated with increased sCD163 levels when adjusted for the interaction with $CD4^+$ cell counts (β = .534 [standard error, .22]; $t = 2.40$; $P = .02$). $CD4^+$ levels were inversely associated with sCD163 levels only among participants with very low food security (β = −.086 [standard error, .03]; $t = -2.60$; $P = .01$).

DISCUSSION

Food insecurity is a social determinant of health that disproportionately affects US minorities [9] and PWH [10] and is associated with several chronic conditions and increased

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Table 1. Characteristics of Study Participants

Characteristic	All Participants (N = 323)	Food-Secure Participants (n = 185)	Food-Insecure Participants (n = 138)	*P* Value
Age, mean (SD), y	56.3 (7.8)	54.0 (7.0)	52.3 (8.8)	.07[a]
Male sex, no. (%)	197 (61.0)	113 (61.1)	84 (60.9)	.97[b]
Race/ethnicity, no. (%)				
Black non-Hispanic	207 (64.1)	123 (66.5)	84 (60.9)	.72[b]
White non-Hispanic	20 (6.2)	10 (5.4)	10 (7.3)	
White Hispanic	65 (20.1)	36 (19.5)	29 (21.0)	
Multiracial/other	31 (9.6)	16 (8.7)	15 (10.9)	
Household size, mean (SD), no. of members	1.9 (1.4)	2.0 (1.4)	1.8 (1.4)	.22[a]
Annual household income, mean (SD), $	13 315 (11 206)	14 211 (12 515)	12 115 (9069)	.08[a]
Household income below federal poverty level, no. (%)	236 (73.1)	137 (74.1)	99 (71.7)	.64[b]
Educational level, no. (%)				
Less than high school	128 (39.6)	66 (35.7)	62 (44.9)	.16[b]
High school or GED degree	98 (30.3)	63 (34.1)	35 (25.4)	
More than high school	97 (30.0)	56 (30.3)	41 (29.7)	
Employment, no. (%)				
Employed	34 (10.5)	21 (11.4)	13 (9.4)	.58[b]
Disabled	205 (63.5)	113 (61.1)	92 (66.7)	
Otherwise unemployed	84 (26.0)	51 (27.6)	33 (23.9)	
Metabolic				
BMI, mean (SD)[c]	29.2 (6.1)	29.4 (6.4)	28.9 (5.7)	.44[a]
Obesity, no. (%)	126 (39.0)	74 (40.0)	52 (37.7)	.67[b]
Hyperglycemia, no. (%)	79 (24.5)	49 (26.5)	30 (21.7)	.33[b]
Hypertriglyceridemia, no. (%)	99 (30.7)	58 (31.4)	41 (29.7)	.75[b]
Hypertension, no. (%)	162 (50.2)	94 (50.8)	68 (49.3)	.79[b]
hs-CRP, mean (SD), mg/L	4.9 (8.9)	4.1 (5.7)	6.0 (11.9)	.08[a]
Substance use, no. (%)				
Hazardous drinking	60 (18.6)	28 (15.1)	32 (23.2)	.07[b]
Cigarette smoking	150 (46.4)	81 (43.8)	69 (50.0)	.267[b]
Cocaine	108 (33.4)	58 (31.4)	50 (36.2)	.36
Cannabis	94 (29.1)	47 (25.4)	47 (34.1)	.09[b]
Heroin	32 (9.9)	17 (9.2)	15 (10.9)	.62[b]
HIV related				
HIV RNA <200 copies/mL, no. (%)	276 (85.5)	163 (88.1)	113 (81.9)	.12[b]
$CD4^+$ cell count, mean (SD), cells/μL	602 (333)	610 (322)	591 (349)	.61[a]
$CD4^+$ cell count <200/μL, no. (%)	23 (7.1)	10 (5.4)	13 (9.4)	.17[b]
Dietary				
Mean value (SD)				
Total energy, kcal	1967 (1150)	1933 (1169)	2012 (1125)	.55[a]
Energy from protein, kcal	327 (208)	332 (228)	321 (178)	.65[a]
Energy from protein, %	17.5 (7.0)	18.0 (7.8)	16.9 (5.9)	.17[a]
Energy from carbohydrate, kcal	925 (631)	916 (629)	938 (635)	.77[a]
Energy from carbohydrate, %	46.7 (13.1)	47.3 (14.1)	45.9 (11.8)	.36[a]
Fiber, g	13.6 (12.3)	12.9 (11.2)	14.6 (13.7)	.25[a]
Energy from fat, kcal	710 (485)	678 (489)	754 (479)	.17[a]
Energy from fat, %	35.6 (11.5)	34.5 (12.3)	37.3 (10.2)	.04[a,d]
SFAs, g	25.3 (21.8)	24.1 (21.8)	27.1 (21.8)	.23[a]
SFAs ≥10% of total energy, no. (%)	172 (53.3)	100 (54.1)	72 (52.2)	.74[a]

Abbreviations: BMI, body mass index; GED, General Educational Development; HIV, human immunodeficiency virus; hs-CRP, high-sensitivity C-reactive protein; SD, standard deviation; SFAs, saturated fatty acids.

[a] *P* value calculated with *t* test.

[b] *P* value calculated with χ^2 test.

[c] BMI was calculated as weight in kilograms divided by height in meters squared.

[d] Significant at $P < .05$.

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Table 2. Distribution of Markers of Immune Activation[a]

Participant Group	Participants, No.	Median Level (IQR), ng/mL		
		sCD14	sCD27	sCD163
All participants	323	1028.5 (801.5–1371.9)	8.5 (6.2–11.4)	541.4 (349.0–961.2)
Food security (standard USDA classification)				
Secure	185	956.9 (731.1–1320.2)	8.1 (5.8–10.5)	532.8 (370.7–874.6)
Insecure[a]	138	1115.2 (843.3–1432.6)	9.3 (6.9–12.1)	551.6 (340.9–1046.4)
P value[b]		.005[c]	.003[c]	.31
Level of food security				
Full	185	956.9 (731.1–1320.2)	8.1 (5.8–10.5)	532.8 (370.7–874.6)
Marginal	53	1042.5 (837.0–1395.8)	9.1 (6.9–11.5)	517.5 (370.7–874.6)
Low	43	1117.8 (909.5–1461.4)	8.9 (6.8–11.6)	567.5 (310.2–968.4)
Very low	42	1171.8 (814.7–1437.8)	9.6 (6.4–13.5)	598.7 (344.5–1070.2)
P value[d]		.050	.051	.75
HIV viral suppression				
Suppressed	276	997.6 (785.9–1335.2)	8.3 (6.0–10.8)	535.7 (343.4–920.7)
HIV RNA >200 copies/mL	47	1184.7 (927.6–1522.8)	10.4 (8.3–13.7)	754.9 (379.3–1207.7)
P value[b]		.009[c]	<.001[c]	.03[c]

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; sCD14, soluble CD14; sCD27, soluble CD27; sCD163, soluble CD163; USDA, United States Department of Agriculture.

[a]The food-insecure group includes participants with marginal, low, or very low food security. The group with full food security is the reference group.

[b]Wilcoxon rank sum tests were performed to compare distributions of sCD14, sCD27, and sCD163 levels; 1-sided *P* values are reported.

[c]Significant at $P < .05$.

[d]Kruskal-Wallis omnibus tests were performed to test for differences in sCD14, sCD27, and sCD163 levels by levels of food security (full, marginal, low, or very low). The Dwass-Steel-Critchlow-Fligner method for pairwise multiple comparisons yielded no significant differences between categories.

mortality rates among US adults [11, 12]. In the current study, we showed a direct association between food insecurity and immune activation among PWH from the MASH cohort, a vulnerable population largely comprising socioeconomically disadvantaged black and Hispanic adults who are engaged in HIV care and virally suppressed. At least some level of food insecurity was reported by nearly half of the participants (43%). Food insecurity was independently associated with increased plasma levels of sCD14 and sCD27, which were also directly correlated with the severity of food insecurity. In addition, very low food security and low $CD4^+$ cell counts, together, predicted higher sCD163 levels. Importantly, immune activation is thought to play a key role in HIV disease progression, as well as in the development and progression of chronic conditions [4, 5]. Our findings, therefore, provide insights into a potential link between food insecurity and adverse health outcomes among low-income PWH who are on suppressive ART.

Notably, the association between food insecurity and sCD14 suggests increased microbial translocation—a major pathway of immune activation in PWH [30]. sCD14 is shed by CD14-expressing monocytes after stimulation by LPS [20]. Consequently, sCD14 is highly correlated with LPS levels [31] and serves as an indirect, yet nonspecific marker of microbial translocation [20, 32]. The poor-quality diets associated with food insecurity may lead to alterations in the diversity of gut microbiota and loss of mucosal barrier defenses, resulting in increased gut permeability and microbial translocation [33]. High-fat diets, in particular, have been shown to alter gut microbiota and disrupt the intestinal barrier, inducing systemic inflammation [18, 34]. In contrast, fiber plays an important role in maintaining gut integrity, as certain undigested carbohydrates are metabolized by gut microbes producing beneficial short-chain fatty acids. While we did not find significant relationships between diet and immune activation, food-insecure participants had higher intake of fat than food-secure participants. In addition, more than half of participants (53%) consumed >10% of total energy from saturated fats, and fiber intake (mean [SD], 13.2 [10.7] g) was well below the recommendations for adults >50 years of age (22.4 g for women and 28 g for men).

The association between food insecurity and sCD27 may have other implications. CD27 is a transmembrane glycoprotein belonging to the tumor necrosis factor receptor family. Although the immunological function of sCD27 has not been fully elucidated, circulating sCD27 induces immunoglobulin G production and is implicated in AIDS-associated lymphoma [24]. Thus, our findings may reflect an increased risk for cancer in association with food insecurity, which is consistent with previous observations [35].

With regard to sCD163, we found that very low food security was associated with increased levels of sCD163 once we accounted for an interaction effect between the severity of food insecurity and $CD4^+$ cell counts. The results therefore suggest that the severity of food insecurity may modify the relationship between immune activation and immunodeficiency in PWH, possibly related to poor engagement in treatment [13, 36].

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Table 3. Univariate Regressions for Markers of Immune Activation in the Miami Adult Studies on HIV Cohort (N = 323)

Variable	sCD14 Levels[a]			sCD27 Levels[a]			sCD163 Levels[a]		
	β Value (SE)	*t* Value	*P* Value	β Value (SE)	*t* Value	*P* Value	β Value (SE)	*t* Value	*P* Value
Age (per 5 y)	.025 (.02)	1.60	.11	.051 (.02)	3.21	.002[b]	.010 (.02)	.39	.69
Sex									
Female	.095 (.05)	1.88	.06	.016 (.05)	.32	.75	.118 (.08)	1.53	.13
Male		Reference			Reference			Reference	
Race/ethnicity									
White non-Hispanic	.204 (.10)	1.96	.05	.232 (.10)	2.21	.03[b]	.385 (.15)	2.49	.01[b]
White Hispanic	.041 (.06)	.65	.52	−.089 (.06)	−1.40	.16	.320 (.09)	3.40	.001[b]
Multiracial/other	−.023 (.09)	−.27	.79	−.118 (.09)	−1.37	.17	.271 (.13)	2.13	.03[b]
Black non-Hispanic		Reference			Reference			Reference	
Income (per $1000)	.001 (.002)	0.25	.81	−.002 (.002)	−.67	.50	.003 (.003)	.77	.44
Household size	.008 (.02)	.46	.64	−.014 (.02)	−.78	.44	−.022 (.03)	−.81	.42
Metabolic									
BMI (per 5 kg/m^2)	.007 (.02)	.34	.73	−.001 (.02)	−.05	.96	.093 (.03)	3.05	.003[b]
Hyperglycemia	−.055 (.06)	−.96	.34	−.086 (.06)	−1.46	.15	.043 (.09)	.49	.62
Hypertriglyceridemia	.104 (.05)	1.95	.05	.090 (.05)	1.64	.10	.173 (.08)	2.13	.03[b]
Hypertension	.083 (.05)	1.69	.09	.129 (.05)	2.57	.01[b]	.013 (.08)	.17	.86
Log hs-CRP level (mg/L)	.055 (.02)	2.62	.009[b]	.039 (.02)	1.81	.07	.019 (.03)	.59	.56
Liver fibrosis[c]	.124 (.05)	2.29	.02[b]	.123 (.05)	2.24	.03[b]	−.060 (.08)	−.73	.47
Substance use									
Hazardous drinking[d]	.068 (.06)	1.07	.29	−.041 (.06)	−.64	.53	.122 (.10)	1.26	.21
Cigarette smoking	.042 (.05)	.85	.40	.086 (.05)	1.71	.09	−.010 (.08)	−1.33	.19
Cocaine	.101 (.05)	1.94	.053	.077 (.05)	1.44	.15	−.028 (.08)	−.35	.73
Marijuana	.070 (.05)	1.29	.20	.041 (.06)	.74	.46	.094 (.08)	1.14	.26
Opioids	.045 (.10)	.45	.65	−.027 (.10)	−.27	.79	−.242 (.15)	−1.63	.11
HIV related									
HIV RNA >200 copies/mL	.143 (.07)	2.04	.04[b]	.271 (.07)	3.87	<.001[b]	.214 (.11)	2.02	.04[b]
CD4$^+$ cell count (per 100/μL)	−.003 (.01)	−.40	.69	−.020 (.01)	−2.75	.006[b]	−.010 (.01)	−.86	.39
Diet									
Energy (per 100 kcal)									
Total	.021 (.02)	.95	.34	−.016 (.02)	−.72	.47	.012 (.03)	.34	.73
Protein	.019 (.01)	1.54	.13	.012 (.01)	1.00	.32	.026 (.02)	1.41	.16
Carbohydrate	.002 (.004)	.61	.54	−.005 (.004)	−1.31	.19	−.0005 (.01)	−.08	.94
Fat	.005 (.01)	.98	.33	−.002 (.01)	−.34	.73	.004 (.01)	.46	.64
SFAs (g)	.008 (.01)	.66	.51	.0001 (.01)	.08	.94	.006 (.02)	.36	.72
Fiber (g)	−.008 (.02)	−.41	.69	−.025 (.02)	−1.21	.23	.016 (.03)	.52	.61
Food insecurity[e]	.132 (.05)	2.66	.008[b]	.120 (.05)	2.38	.02[b]	.022 (.08)	.29	.77

Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus; hs-CRP, high-sensitivity C-reactive protein; sCD14, soluble CD14; sCD27, soluble CD27; sCD163, soluble CD163; SE, standard error; SFAs, saturated fatty acids.

[a]Univariate linear regressions were performed to assess potential predictors of (log-transformed) sCD14, sCD27, and sCD163 levels, measured in nanograms per milliliter.

[b]Significant at $P < .05$.

[c]Liver fibrosis defined as fibrosis 4 index score ≥1.45.

[d]Hazardous drinking defined as Alcohol Use Disorders Identification Test (AUDIT) score ≥8.

[e]Food-insecure group includes participants with marginal, low, or very low food security. The group with full food security is the reference group.

These findings further support a role of microbial translocation, because LPS promotes shedding of sCD163 in plasma [37]. Interestingly, very low food security was associated with not having a suppressed viral load, but not with CD4$^+$ cell counts.

The findings in the current report are consistent with previous research. Population-based studies have established an association between food insecurity and CRP, a marker of systemic inflammation [16, 17]. Notably, Gowda et al [16] showed that the relationship between food insecurity and CRP was partially mediated by elevated white blood cell counts, suggesting a potential role of immune activation.

In recent years, food insecurity has been associated with elevated inflammation (interleukin 6 and tumor necrosis factor receptor 1) [18], as well as CD4$^+$ and CD8$^+$ activation (percentage CD38$^+$HLADR$^+$) and other markers of immune dysregulation (percentage CD57$^+$CD28$^-$ and CD57$^-$CD28$^+$) in women living with HIV who were mostly virally suppressed [19]. These results, as well as those reported herein, point to biological

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Table 4. Relationship Between Food Insecurity and Immune Activation, Controlling for Demographic, Dietary, Clinical, and Behavioral Factors (N = 323)

	sCD14 Levels[a]			sCD27 Levels[a]			sCD163 Levels[a]		
Model	β Value (SE)	*t* Value	*P* Value	β Value (SE)	*t* Value	*P* Value	β Value (SE)	*t* Value	*P* Value
1. Food insecurity[b] (univariate)	.132 (.05)	2.66	.008[c]	.120 (.05)	2.38	.02[c]	.022 (.08)	.29	.77
2. Adjusted for sociodemographic characteristics, HIV viral load, and CD4$^+$ cell count[d]	.135 (.05)	2.73	.007[c]	.122 (.05)	2.50	.01[c]	−.004 (.07)	−.06	.96
3. Also adjusted for diet[e]	.138 (.05)	2.65	.009[c]	.128 (.05)	2.54	.01[c]	.009 (.08)	.12	.91
4. Also adjusted for metabolic parameters and substance use[f]	.117 (.05)	2.25	.02[c]	.129 (.05)	2.56	.01[c]	.024 (.08)	.31	.76

Abbreviations: HIV, human immunodeficiency virus; sCD14, soluble CD14; sCD27, soluble CD27; sCD163, soluble CD163; SE, standard error.

[a]A series of multiple linear regression models was performed to assess the relationship between food insecurity and (log-transformed) sCD14, sCD27, and sCD163 levels, measured in nanograms per milliliter, with adjustment for potential confounders.

[b]Food-insecure group includes participants with marginal, low, or very low food security. The group with full food security is the reference group.

[c]Significant at $P < .05$.

[d]Characteristics/parameters included age, sex, race/ethnicity, income, household size, HIV viral load >200 copies/mL, and CD4$^+$ cell count.

[e]Diet parameters included total energy (in kilocalories), energy from protein, carbohydrates, and fats (in kilocalories), saturated fats (in grams), and fiber (in grams).

[f]Metatolic parameters included body mass index, hyperglycemia, hyperlipidemia, hypertension, liver fibrosis (fibrosis 4 index score ≥1.45), high-sensitivity C-reactive protein level, hazardous drinking, cigarette smoking, cocaine use, and opioid use.

pathways between food insecurity and chronic disease. For example, among Latinos with type 2 diabetes, increased stress (cortisol) and inflammation (CRP) partially mediated the relationship between food insecurity and insulin resistance, the precursor for type 2 diabetes [38]. In another study, food insecurity was associated with the primary allostatic system (neuroendocrine and inflammatory), which incorporated serum cortisol and CRP as biomarkers of stress and inflammation, respectively [39]. Although our data did not show an association between food insecurity and hs-CRP, hs-CRP was correlated with sCD14 and showed a trend with sCD27.

Diet quality may explain some of the relationship between food insecurity, immune activation and inflammation, and chronic disease. Indeed, food insecurity often leads to dependence on low-cost foods, resulting in poor-quality diets that are high in fats, simple sugars, and refined carbohydrates but low in essential nutrients and fiber [8]. Micronutrients play critical roles in immunity and their deficiency can contribute to immune activation and inflammation. Moreover, Bergmans et al [15] reported on the association between food insecurity and inflammatory potential of the diet, showing a dose-response relationship between the severity of food insecurity and the Dietary Inflammatory Index scores. In our study, we found that levels of sCD14 and sCD27 were directly correlated with the severity of food insecurity. One may surmise that as the severity of food insecurity increases, so does the immunoinflammatory potential of the diet.

However, diet alone does not entirely explain the relationship between food insecurity and health outcomes. Other potential mechanisms include poor disease management [36, 40], chronic stress [38], and competing financial constraints, such as having to make tradeoffs between food and medication [41] while having increased healthcare expenditures [42]. Food insecurity is also associated with high rates of substance use [43, 44], which may also contribute to poor health. Indeed, we observed trends between cigarette smoking and sCD27 levels, as well as between cocaine use and sCD14 levels. Both smoking and cocaine have been associated with immune activation in PWH [45, 46].

To summarize, food insecurity was associated with increased biomarkers of immune activation sCD14, sCD27, and sCD163 in PWH from the MASH cohort. The present study is strengthened by the use of validated assessments among a well-characterized cohort of PWH. While we controlled for intake of energy, macronutrients, saturated fatty acids, and fiber, future studies may consider the impact of diet quality and microbial translocation on the relationship between food insecurity and immune activation. The cross-sectional design does not allow establishment of causality, and it is possible that some of the effects observed may be related to unmeasured factors. However, our findings remained consistent even after controlling for several sociodemographic and comorbid confounders. Our findings are also consistent with findings of prior research. Longitudinal studies may provide a more thorough understanding of the causal and temporal relationships between food insecurity, immune activation, and chronic disease outcomes.

Food insecurity is a key social determinant of health, and a growing body of research continues to shed light on its pervasive effects on vulnerable populations. Standardized screening for food insecurity in low-income clinical settings may prove advantageous in relieving disease burden through early identification and intervention. Indeed, healthcare providers can play a critical role in addressing food insecurity by recognizing its role in health and well-being and taking active steps toward incorporating it into their practice. Some recommend using the "SEARCH" approach (screen, educate, adjust, recognize, connect, and help) [47]. However, many healthcare providers fear

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that screening for food insecurity may damage the patient's relationship with the provider and reduce patient satisfaction [48]. Others may not recognize food insecurity as a medical problem. However, the most likely barrier to screening appears to be concerns about not knowing how to manage food insecurity [48]. It may be that food insecurity interventions should start at the clinician level by increasing awareness, knowledge of available resources, and self-efficacy in managing patients' food insecurity. Indeed, there is a great need for high-quality research on healthcare-based food insecurity interventions [49]. The findings of the current study have further implications for HIV care providers, because immune activation can contribute to HIV disease progression and affect the outcome of comorbid conditions.

Public health strategies to curve food insecurity are also needed. Participation in the Supplemental Nutrition Assistance Program (SNAP)—the largest food-assistance program in the United States—is often insufficient to relieve monetary constraints. Although most eligible individuals participate in this program, the current criteria for eligibility prevent many from obtaining this benefit. Furthermore, some have recently argued that while food insecurity has been increasingly recognized, the aspect of nutrition within food security has been largely overlooked [50]. For example, food security assessments rarely evaluate nutritional status and diet quality. Rather, these authors call for a shift in focus toward "nutrition security" [50].

In conclusion, food insecurity was associated with markers of immune activation in the MASH cohort, suggesting a biological link between food insecurity and chronic disease among PWH. Our findings suggest that improving financial security, access to high-quality foods, and nutrition knowledge could lead to significant health benefits in this highly vulnerable population. In addition, screening for food insecurity may be a cost-efficient method of risk assessment and reducing the high burden of disease among PWH. Mechanisms for the effect of food insecurity on immune activation remain to be elucidated. Future research should consider diet quality and gut permeability as potential mediators of food insecurity and immune activation.

Notes

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