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# Repeated assessments of food security predict CD4 change in the setting of antiretroviral therapy

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## Abstract

Food insecurity is highly prevalent in HIV-infected populations, and analyses utilizing multiple assessments of food security to predict CD4 change are lacking. 592 patients with ≥ 4 food security assessments were followed prospectively. In the final model, for patients using antiretroviral therapy, increases in CD4 counts were on average 99.5 cells less for individuals with at least one episode of food insecurity compared to those consistently food secure ($P < 0.001$). Other sociodemographic factors were not predictive. Repeated assessments of food security are potent predictors of treatment response notwithstanding antiretroviral therapy use. Potential mechanisms for this association are proposed.

### Keywords

Food security; Immunological response; Antiretroviral therapy

## Background

In 1990, an expert panel of the American Institute of Nutrition defined food insecurity as "existing whenever the availability of nutritionally adequate and safe foods or the ability to acquire acceptable foods in socially acceptable ways is limited or uncertain."[1] North American surveys of the general population report a 9–11% prevalence of food insecurity.[2] In contrast, HIV-infected populations consistently report food insecurity at higher rates: Atlanta 52%,[3] San Francisco 49%,[4] and, 48% and 71% in two Canadian surveys.[5,6]

Characteristics of HIV-infected patients associated with food insecurity include poverty, other markers of low socioeconomic status (SES), intravenous drug use (IDU) and depression.[4–7] Within the same cohort of HIV-infected subjects as our present study, the Nutrition for Healthy Living (NFHL) cohort, food insecure men were more likely to have a diet characterized by more fast food and less fruits and vegetables.[8] Additionally, food

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insecurity has been associated with worse outcomes on antiretroviral therapy (ART), including worse adherence, incomplete virological suppression and lower survival.[3,4,9] Associations with immunological responses have only been reported cross-sectionally and analyses involving repeated measure of food security are not reported.[3,6,9] We examined the ability of multiple measures of food security to predict CD4 T-cell response in the NFHL cohort.

## Methods

We examined NFHL participants enrolled from 1995–2005 who completed 4 or more study visits. This prospective cohort investigated the causes and consequences of nutritional and metabolic abnormalities on HIV-infected adults in the Boston and Providence area. Individuals were excluded if they were pregnant, diabetic, or suffering from thyroid disease or cancer. Biannual study visits obtained information on clinical status, drug use, SES and HAART use. $CD4^+$ T-cells were counted using flow cytometry, and HIV RNA was measured by the Amplicor Monitor RT-PCR assay (Roche Molecular Systems) with a lower detection limit of 2.6 $\log_{10}$ copies/mL (400 copies/mL). Further details on data collection and subject selection have been previously reported.[10,11]

Food Security was defined using the adult individual food security scale questions originally derived by Radimer et al[12] but later modified by Kendall et al[13]. This scale included three questions ("I eat less than I think I should because I don't have enough money for food", "I can't afford to eat properly", and "I am often hungry, but I don't eat because I also can't afford enough for food"). The fourth question ("I eat the same thing for several days in a row because I don't have enough money to buy different things") was adapted by Kendall et al from the qualitative component of the adult household food security scale.[13] Subjects answering "Often true" or "Sometimes true" to any question were food insecure for that visit. For the dichotomous variable in this analysis, subjects who were insecure on one or more visits were defined as food insecure and those secure at every visit were defined as food secure. A trichotomous variable was also created for subjects who were always food insecure, partially food insecure (insecure at ≥ 1 visit but not all visits), and always food secure. Thus, repeated measures of food security were used to create food security variables for this analysis. Poverty was defined as total household income below the annual federal poverty line or personal annual income below $10,000.[14]

Baseline characteristics were compared by food security status. Chi-square, Student's t, and Wilcoxon rank-sum tests were used as appropriate. Univariate and multivariate linear regression was performed for the dependent variable CD4 T-cell change from baseline to last study visit. Independent variables were: age, gender, race (white or non-white), cumulative years of HAART at final study visit, history of IDU up to final study visit, mean BMI over period observed (<20, 20–25, >25 $kg/m^2$), poverty at final study visit, and food insecurity (one of the variables as previously defined, or baseline food insecurity). Variables with $P < 0.2$ in univariate analyses were entered into the multivariate model. Variables not reaching statistical significance ($P < 0.05$) were deleted from the model. A multivariate model excluding participants who never received HAART was performed as a sensitivity analysis. Interaction terms between BMI categories and food security were examined. All analyses were conducted using SAS v9.2 (SAS Institute, Cary, NC).

## Results

Table 1 shows baseline characteristics of participants by food security status. The cohort comprised 592 subjects with a mean age of 40.6±7.5 years of whom 70% were male and 29% had a history of IDU. 217 (37%) were chronically food secure and 375 (63%) were assessed as food insecure on one or more occasions. Of the food insecure, 51 (14%) were insecure at every study visit, 137 (37%) at 50 to <100% of visits and 187 (50%) were insecure at <50% of visits. Food secure individuals had shorter median duration of follow up (4.4 years [IQR 2.9–7.4] vs 6.0 years [IQR 3.3–7.8], $P$ <0.01), and at baseline were less likely to have a history of IDU (14.8% vs 47.7%, $P$ <0.001) and had lower BMI (25.0 vs 26.4, $P$ = 0.01). Baseline CD4 T-cell counts were not significantly different between groups (311 vs 342 cells/μl, $P$ = 0.08).

Parameter estimates from regression models are presented in Table 2. Cumulative years of HAART was significantly associated with a positive change in CD4 count (41.3 cell greater change / additional year of HAART), while history of IDU, not being white, poverty and food insecurity predicted negative changes in CD4 over the period observed. In the multivariate model using the dichotomous food insecurity variable cumulative HAART use remained a potent predictor of CD4 change (40.3 cell greater change / additional year of HAART, $P$ <0.001) with the only additional covariate remaining in the model being food insecurity (99.5 cell less change over the period observed, $P$ <0.001). On the basis of this model a patient who was food secure and received 5 years of HAART would expect a $[-8.04 + (40.36 \times 5)] = 194$ CD4 cell increase, but if food insecure, only a $[-8.04 + (40.36 \times 5) - 99.52] = 94$ CD4 cell increase. In an alternative multivariate model where food security is trichotomized, those who were partially and always insecure had similar parameter estimates for CD4 change (110.2, $P$ <0.001, and 95.1, $P$ =0.03, cells less change respectively). Additionally, baseline food security was not predictive of CD4 change in multivariate models. In a sensitivity analysis excluding 67 individuals who did not receive HAART, the multivariate model contained both cumulative HAART (31.5 cell greater change / additional year of HAART, $P$ <0.001), food insecurity (76.4 cell less change over the period observed, $P$ =0.004) and history of IDU (64.8 cell less change over the period observed, $P$ =0.02).There was no evidence of interaction between BMI categories and food security in multivariate models.

## Discussion

This is the first study to describe the predictive ability of food insecurity on changes in CD4 counts over time in an HIV-infected population, and the first study to document clinical outcomes with repeated measures of food security. These observations persist while controlling for duration of HAART use and SES variables (poverty, race and IDU) that have been previously studied within this and other observational cohorts.[15–17]

First, this study demonstrates an astonishing rate of food insecurity in this HIV infected cohort, the composition of which reflects the epidemic as it currently exists. Further, this study reveals multiple baseline characteristics associated with food insecurity, not all of which are consistent with previous reports. HAART, CD4 and HIV viral load at baseline were not significantly associated with food insecurity, in contrast to a history of IDU, being female and non- white, which were all significantly more prevalent in the food insecure. Similar associations between food security status and IDU or gender have been reported in a Canadian cohort[5,6] but not elsewhere for HIV-infected individuals.[3,7] Baseline BMI was higher in this study for food insecure subjects, a finding not replicated in HIV-infected populations but reported in non-HIV-infected subjects.[18,19] The finding of elevated BMI is consistent with prior data from this cohort where food insecure individuals consumed more fast food than the food secure.[8]

Not surprisingly, cumulative years of HAART strongly predicted CD4 response in univariate and multivariate regression models. The parameter estimate of a roughly 40 cell increase in CD4 count per year of HAART is consistent with other large observational cohorts over similar periods of follow up.[20–22] Importantly, individuals meeting criteria for food insecurity as defined here could have a 100 CD4 T-cell count deficit even in the setting of HAART. Therefore, it is plausible that food insecure individuals are at increased risk for opportunistic infections and other complications of lower CD4. Furthermore, the finding that partially and chronically insecure individuals have a similar negative impact on CD4 response suggests that repeated assessments of food security status to detect even a single assessment of insecurity could be important to identify individuals at risk for poor immunological outcomes. The finding of high levels of food insecurity in this and other HIV-infected cohorts combined with the deleterious impact on immunological outcomes may explain why some individuals experience more HIV-related complications and increased mortality despite HAART.[23] It is also noteworthy that using baseline food security status alone was not predictive of CD4 change, suggesting that regular assessments of food security status are more accurate to detect individuals at risk for poor treatment outcomes. Using the CD4 change outcome not only allows us to examine how food security predicts treatment response over time, but also to account for potential differences in baseline CD4 previously reported in cross-sectional analyses.[3,5–7] In contrast to previous data, baseline CD4 in this cohort did not differ by food security status, with only a trend ($P = 0.08$) towards higher baseline CD4 in the food insecure. Reasons for this trend are unclear but could reflect a longer duration of infection for individuals infected earlier in the course of the US epidemic, such as men who have sex with men.

The mechanism by which these associations are mediated is unclear but several possibilities exist. Food insecurity may be a marker of poor access to care, potentially leading to inadequate therapy and subsequent poor immunological response. Food insecurity may also be associated with the presence of socio-behavioral issues such as depression, high risk sexual behavior, drug use and recent incarceration.[6,7,24], which may manifest as poor adherence[3,4,9] leading to lower CD4. Notably, food insecurity has been linked with poor adherence due to fear of antiretroviral toxicity in the absence of food, and the competing demands between food, and resources to obtain health care.[3,7] Finally, food insecurity may influence nutritional quality. As previously mentioned, food insecure participants consumed more fast foods and less fruit and vegetables.[8] Micronutrient deficiencies have been associated with lower CD4,[25] while multivitamin supplementation has been reported to improve immunological responses.[26] Thus poor quality diet could conceivably impact CD4 response via micronutrient deficiencies. Lastly, a combination of both social and nutritional issues may underlie the mechanism of this association.

This study had several strengths and limitations. Food security status was assessed at every study visit but to be insecure for this analysis subjects had to complete at least 4 study visits and be insecure on one or more occasions. This definition of food security status was a robust predictor of CD4 change implying that chronically food secure individuals are a distinct population for improved treatment response compared to those with one or more episodes of food insecurity over multiple years. In addition, controlling for HAART and factors associated with low SES allows us to draw additional inference about food security as an independent predictor of treatment outcomes. A limitation of this study is that it may not be generalizable to all settings due to regional differences in HIV epidemiology. However, government funding was available for HIV-infected patients to receive medical care and ART throughout the study.[27]

In summary, food insecurity is a potent predictor of poor immunological response even in the setting of HAART. Regular assessments to identify food insecure individuals and interventions to alleviate food insecurity could prove valuable to improve immunological outcomes for a large number of individuals living with HIV.

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**Table 1**

Baseline characteristics

| | Food Secure[b] 217 (36.7) | Food Insecure[a] 375 (63.3) | Total 592 | p-value[c] |
|---|---|---|---|---|
| Mean age in years | 41.7 ± 8.4 | 39.9 ± 6.8 | 40.6 ± 7.5 | 0.006 |
| Gender | | | | <0.001 |
| Female | 40 (18.4) | 136 (36.3) | 176 (29.7) | |
| Male | 177 (81.6) | 239 (63.7) | 416 (70.3) | |
| Race | | | | <0.001 |
| White | 169 (77.9) | 164 (43.7) | 333 (56.3) | |
| Non white | 48 (22.1) | 211 (56.3) | 259 (43.8) | |
| IDU | | | | <0.001 |
| Active or past IDU | 32 (14.8) | 179 (47.7) | 211 (35.6) | |
| Never IDU | 185 (85.3) | 196 (52.3) | 381 (64.4) | |
| HAART | | | | 0.08 |
| On HAART | 112 (55.2) | 163 (47.7) | 275 (50.5) | |
| Not on HAART | 91 (44.8) | 179 (52.3) | 270 (49.5) | |
| BMI[d], kg/$m^2$ | 25.0 ± 4.1 | 26.4 ± 5.5 | 25.9 ± 5.1 | <0.001 |
| CD4, counts/mL | 311 (176–484) | 342 (189–568) | 332 (182–533) | 0.08 |
| $Log_{10}$ HIV viral load, copies/mL | 3.4 (ND[e]-4.4) | 3.5 (ND[e]-4.5) | 3.4 (ND[e]-4.5) | 0.38 |

Note: Sample size varied based on missing data but no more than 2% data missing, except for HAART use (n=545) and viral load (n=555)

Values represent n (% with that characteristic), median (Q1-Q3) or mean ± SD.

[a]Food insecure at one or more study visits

[b]Food secure at all study visits

[c]p-values chi-square (categorical),Student t-test (continuous normal distribution), Wilcoxon rank sum test (continuous non-normal distribution)

[d]Body mass index

[e]ND = Not Detectable. Lower limit of detection 2.6 $log_{10}$ (400) copies/mL

**Table 2**

Single and multiple linear regression for CD4 T cell change from baseline to final study visit

| | Univariate Model Parameter Estimate | p-value | Multivariate Model 1 Parameter Estimate[a] | p-value | Multivariate Model 2 Parameter Estimate[b] | p-value |
|---|---|---|---|---|---|---|
| Intercept | | | −8.04 | | −8.13 | |
| Age – increase by 1 year | 2.73 | 0.09 | - | - | - | - |
| Cumulative years of HAART – increase by 1 year | 41.34 | <0.001 | 40.36 | <0.001 | 40.38 | <0.001 |
| Active or past IDU | −101.02 | <0.001 | - | - | - | - |
| Gender (being female) | −41.98 | 0.14 | - | - | - | - |
| Race (not being white) | −60.47 | 0.02 | - | - | - | - |
| Poverty[c] at final visit | −90.77 | <0.001 | - | - | - | - |
| Mean BMI[d] > 25 | Ref | - | - | - | - | - |
| Mean BMI 20 – 25 | 11.57 | 0.65 | - | - | - | - |
| Mean BMI < 20 | −82.33 | 0.16 | - | - | - | - |
| Food insecure[e] | −111.84 | <0.001 | −99.52 | <0.001 | | |
| Food secure[f] | Ref | | | | Ref | |
| Partially food insecure[g] | −121.16 | <0.001 | | | −100.18 | <0.001 |
| Always food insecure[h] | −110.45 | 0.01 | | | −95.07 | 0.03 |

**Note:**

[a] Dichotomous definition of food security

[b] Alternative model using a trichotomous definition of food security

[c] Total household income below federal poverty line or personal annual income < $10,000

[d] Body mass index average over all study visits in kg/ $m^2$

[e] Food insecure at 1 or more study visits

[f] Food secure at all study visits

[g] Food insecure at 1 or more, but not all, study visits

[h] Food insecure at all study visits

HAART – Highly active antiretroviral therapy; IDU – Intravenous drug use