Higher Body Mass Index Is Associated With Greater Proportions of Effector CD8+ T Cells Expressing CD57 in Women Living With HIV

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Background: A low proportion of $CD28^-CD8^+$ T cells that express CD57 is associated with increased mortality in HIV infection. The effect of increasing body mass index (BMI) changes in the proportion of $CD57^+CD28^-CD8^+$ T cells among HIV-infected individuals on antiretroviral therapy is unknown.

Setting: In a US cohort of HIV-infected women, we evaluated associations of BMI and waist circumference with 3 distinct $CD8^+$ T cell phenotypes: % $CD28^-CD57^+CD8^+$ T cells, % $CD57^+$ of $CD28^-CD8^+$ T cells, and % $CD28^-$ of all $CD8^+$ T cells.

Methods: Multivariable linear regression analysis was used to estimate beta coefficients for each of 3 T-cell phenotypes. Covariates included HIV parameters (current and nadir CD4, current viral load), demographics (age, race, income, and study site), and lifestyle (tobacco and alcohol use) factors.

Results: Of 225 participants, the median age was 46 years and 50% were obese (BMI >30 m^2/kg). Greater BMI and waist circumference were both associated with higher % $CD28^-CD57^+CD8^+$ T cells and % $CD57^+$ of all $CD28^-CD8^+$ T cells in multivariable analysis, including adjustment for HIV viral load (all $P < 0.05$). The

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association between greater BMI and the overall proportion of $CD28^-$ $CD8^+$ cells in fully adjusted models (0.078, 95% confidence interval: −0.053 to 0.209) was not significant.

Conclusions: In this analysis, greater BMI and waist circumference are associated with greater expression of CD57 on $CD28^-CD8^+$ T cells and a greater proportion of $CD57^+CD28^-$ $CD8^+$ T cells. These findings may indicate that increasing BMI is immunologically protective in HIV-infected women. Future research is needed to understand the prognostic importance of these associations on clinical outcomes.

Key Words: HIV, obesity, WIHS, CD57, immune senescence

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INTRODUCTION

The advent of highly active antiretroviral therapy (ART) has had a profound impact on HIV-associated morbidity and mortality.[1] Although the prevalence of HIV-associated wasting has declined, the proportion of overweight and obese HIV-infected individuals is increasing.[2] Although recent studies have failed to show a consistent effect for obesity in the pathogenesis of cardiovascular disease in HIV-infected individuals,[3,4] there is evidence demonstrating that obese HIV-infected individuals have a greater prevalence of metabolic diseases, including type 2 diabetes mellitus, compared with nonobese persons.[5–7] In addition, increasing body mass index (BMI) is associated with greater innate and adaptive immune activation, even in the setting of treated HIV infection.[8,9] As observed in the general population,[10] serum levels of systemic markers of inflammation such as C-reactive protein and tumor necrosis factor alpha[11–13] are higher among HIV-infected adults with greater adiposity. There is also evidence that adiposity influences adaptive immune responses, with several recent studies suggesting that obesity independently influences immunologic recovery in individuals initiating ART.[14–17]

Whether increasing BMI also influences the development of other immune defects in HIV-infected individuals is less clear. Studies have demonstrated that HIV infection leads to numerous $CD8^+$ T-cell abnormalities, some of which are also seen in elderly populations (eg, an expansion of $CD28^-$ $CD8^+$ T cells) and some of which are distinct from those observed in the elderly (eg, decreased terminal differentiation and a reduced proportion of $CD28^-CD8^+$ T cells that express CD57).[18,19] It is possible that increasing adiposity may further affect T-cell differentiation because of elevations in systemic low-grade inflammation, heightened oxidative stress,[20] alterations in nutrition and micronutrients,[21,22] psychosocial factors such as depression and poor quality of life,[23] or perturbations in serum concentrations of leptin, which has been shown to influence T-cell activation and proliferation.[24]

The aim of our study was to investigate the relationship between BMI and $CD8^+$ T-cell phenotypes that have been previously linked to mortality in a diverse cohort of HIV-infected women, while adjusting for potential confounders such as socioeconomic factors, lifestyle and behavioral variables, and HIV viral load. Given the numerous deleterious inflammatory and metabolic sequelae of obesity,[9,11] we hypothesized that greater BMI would be associated with a pattern of poor $CD8^+$ T-cell differentiation in HIV-infected adults that has been previously associated with mortality in this setting.

METHODS

Study Design and Population

The Women's Interagency HIV Study (WIHS) is a large, multicenter, ongoing prospective cohort of HIV-infected and at-risk women in the United States,[25,26] established in 1993. At semiannual visits, participants are interviewed and examined, and serum specimens are collected and stored in a −80°C freezer. The enrolled women are representative of US women living with HIV in terms of demographic and clinical parameters.[25] Specifically, this investigation was a cross-sectional study of WIHS women enrolled in the WIHS Food Insecurity Substudy from 6 US WIHS sites (Bronx, Brooklyn, Chicago, Los Angeles, San Francisco, and Washington, DC) who were seen from April 2013 to September 2013. Our analysis was limited to HIV-infected participants who were on ART and did not have diagnoses of cancer, autoimmune diseases, or hepatitis B or C virus infection. All participants were fasting for laboratory studies.

Laboratory Methods

T-cell immune senescence was characterized by polychromatic flow cytometry on frozen/thawed peripheral blood mononuclear cells at Rush University Medical Center (Landay lab). Thawed cells were stained for cell viability with the Aqua Live/Dead cell stain kit (Invitrogen, Carlsbad, CA) before cell surface staining. Cell surface markers were stained with fluorochrome-conjugated monoclonal antibodies to CD3, CD4, CD8, CD28, and CD57 (BD Biosciences, San Jose, CA). Cells were acquired within 24 hours on a LSR2 flow cytometer using BD FACSDiva software (BD Biosciences). Analysis of flow cytometry data was performed using FlowJo software (Ashland, OR). Immune senescence ($CD57^+$\$CD28^-$) analysis was performed and reported on singlet live (Aqua-) $CD3^+$\$CD8^+$ T cells.

Predictor

The primary predictor in this study was BMI (continuous in kg/m^2) measured at the visit closest to the visit where serum was obtained for testing of cellular immune markers. We also examined BMI as a categorical measure with obesity defined as BMI >30 kg/m^2. Anthropometric characteristics included waist circumference (in cm), hip circumference (in cm), and hip-to-waist ratio which were also included as predictors.

Outcome

The primary outcomes of interest were the $CD8^+$ T-cell phenotypes that characterize immunosenescence, specifically 3 separate $CD8^+$ T-cell phenotypes: the proportion of $CD8^+$ T lymphocytes that were $CD28^{-}CD57^{+}$, the proportion of $CD8^{+}CD28^{-}$ expressing CD57, and the proportion of $CD8^{+}$ T lymphocytes that were $CD28^{-}$ of the total $CD8^{+}$ T lymphocyte population. Each of these 3 phenotypes was considered as individual outcomes and measured continuously in cells/μL. The first T-cell phenotype in our analysis, % $CD28^{-}$ $CD57^{+}$ of $CD8^{+}$ T cells, was calculated as the summation of 2 distinct $CD8^{+}$ T-cell populations identified on flow cytometry, namely the proportion of $CD8^{+}$ T lymphocytes that were $CD57^{-}$ $CD28^{-}$ and the proportion that were $CD57^{+}$ $CD28^{-}$. The second T-cell phenotype, % $CD57^{+}$ of $CD28^{-}$ of $CD8^{+}$ T cells, was reported output from the flow cytometry. The third output was derived from dividing proportion of $CD28^{-}$ $CD57^{+}$ of $CD8^{+}$ T cells by the proportion $CD28^{-}$ of $CD8^{+}$ T cells that were expressing CD57.

Covariates

Candidate covariates included sociodemographic factors: age (in years at the visit), ethnicity (non-Hispanic white, African American, Hispanic, or other), educational attainment (less than high school, completed high school, some college or greater), employment status (employed or not), annual income (less than or equal versus greater than $30,001), and study site (Bronx and Brooklyn, NY, Washington, DC, Chicago, IL, and San Francisco, CA). Lifestyle factors considered were as follows: smoking (none, current, or past), smoking duration (in years smoked), and alcohol use (none; light drinking, defined as consumption of 1–15 g of alcohol/d, moderate drinking, defined as consumption of 15–30 g alcohol/d; or heavy drinking, defined as >30 g/d). HIV-related factors included the following: current $CD4^{+}$ T-cell count (in cells/mm^3), nadir $CD4^{+}$ T-cell count (in cells/mm^3), HIV viral load (log transformed in copies/mL), history of clinical AIDS, and current use of ART. Variables were selected by a priori consideration of confounders on the relationship between BMI and the outcomes of interest, informed by previous literature.[15,27,28] Height was included as a covariate because use of height squared as the denominator of BMI does not completely adjust for height.[29] CMV serostatus was not available for inclusion in the analysis, although based on other analyses performed in the WIHS cohort, we anticipate that prevalence of CMV seropositivity was very high.[30]

Statistical Analysis

Summary statistics were obtained for covariates. We compared sociodemographic and clinical characteristics within each of the 3 $CD8^{+}$ T-cell phenotypes using the Kruskal–Wallis test for continuous variables and the Fisher exact test for categorical variables. All continuous covariates were standardized by dividing by the interquartile range (IQR) to improve comparison and interpretation. Given the exploratory nature of this study, stepwise model building was used to select among the available covariates, retaining only those variables with $P < 0.2$, and was performed individually for each of the 3 outcomes. Linear regression models were used to estimate beta coefficients for the primary predictor and covariates selected by stepwise modeling, on each of the outcomes. An alpha of 0.05 was selected as the significance threshold. All analyses were conducted using STATA (version 13; StataCorp, College Station, TX). In an additional sensitivity analysis, separate models restricted to those with an undetectable viral load (defined as <20 or 48 copies/mL depending on the timing of the specimen) were also constructed to control for the immunologic effect of persistent viremia.

Finally, in separate models, we evaluated other anthropometric measures as primary predictors of $CD8^{+}$ T-cell phenotypes. In models controlling for demographic, lifestyle factors, and HIV-specific variables, we determined the association of waist circumference and waist-to-hip ratio with each of the $CD8^{+}$ T-cell phenotypes. In each case, fully adjusted models that did and did not adjust for HIV viral load were compared to determine the extent to which HIV viremia attenuated associations between body composition parameters and $CD8^{+}$ T-cell phenotypes.

Ethics Statement

All participants provided written and informed consent for participation in the WIHS. The research conducted as part of the WIHS was approved by institutional review boards at all study sites. All studies were conducted according to the principles outlined in the Declaration of Helsinki.

RESULTS

We present data on 225 women included in this analysis. Most participants identified as black (Table 1). The median age was 46.5 years. Nearly two-thirds of the participants had an annual income of less than $30,000 and had completed 12 or fewer years of education. The median BMI was 30 kg/m^2. More than 3 quarters of study participants were classified as overweight and 50% were either obese or morbidly obese. The median duration of ART therapy was 13 years. The majority (74%) of participants had an undetectable viral load. The median current CD4 T-cell count was 626 cells/mm^3, and the median CD4 T-cell count nadir was 310 cells/mm^3.

Association of Body Composition Parameters With $CD8^{+}$ Phenotypes

There were significant positive correlations between increasing BMI and the proportion of $CD8^{+}$ cells that were $CD28^{-}CD57^{+}$ ($r = 0.187$, $P < 0.05$) (Fig. 1A) and the proportion of $CD28^{-}$ $CD8^{+}$ T cells expressing $CD57^{+}$ ($r = 0.185$, $P < 0.05$) (Fig. 1B), but not the overall proportion of $CD28^{-}$ $CD8^{+}$ T cells ($r = 0.053$, $P = 0.418$) (Fig. 1C). Neither current CD4 count (Fig. 1D) nor HIV viral load (Fig. 1E) were correlated with BMI ($R = 0.021$, $P = 0.746$ and $R = -0.08$, $P = 0.221$, respectively).

In regression analysis, each IQR increase in BMI was associated with a significantly greater proportion of

TABLE 1. Demographic and Clinical Characteristics Among 225 Women With HIV Infection

Variables	N (%)*
Demographic variables	
Age in yr (IQR)	46 (41–51)
Site, n (%)	
Bronx	28 (12)
Brooklyn	82 (34)
Georgetown	59 (24)
San Francisco	11 (4)
Chicago	62 (26)
Race, n (%)	
Non-Hispanic white	25 (10)
Black/African American	173 (71)
Hispanic	32 (13)
Other	11 (6)
Income, n (%)	
≤\$30,000	144 (63)
>\$30,001	84 (37)
Education, n (%)	
Less than high school	79 (33)
Completed high school	71 (29)
Some college or greater	91 (38)
Employment status, n (%)	
Employed	132 (55)
Unemployed	109 (45)
Lifestyle variables, n (%)	
Current smoker	71 (29)
Smoking history, yr median (IQR)	6.5 (0–24)
Alcohol consumption, n (%)	
None	126 (53)
>0–7 drinks/wk	100 (41)
>7–12 drinks/wk	5 (2)
>12 drinks/wk	9 (4)
Body composition variables	
Hip circumference, cm (IQR)	108 (14.65)
Waist circumference, cm (IQR)	98 (88–112)
Height, cm (IQR)	162 (158–167)
BMI, m/kg^2 (IQR)	30 (25–36)
HIV parameters	
Current CD4 count, median (IQR)	626 (456–834)
Nadir CD4 count, median (IQR)	310 (173–461)
Log viral load, median (IQR)	3.00 (3.0–3.18)
Viral suppression	178 (74%)
Duration on HAART, yr (IQR)	13 (6–15)

*Data are median (IQR) values, unless otherwise indicated.

CD28$^-$CD57$^+$ of CD8$^+$ T cells [0.184, 95% confidence interval (CI): 0.06 to 0.307] and a greater proportion of CD28$^-$CD8$^+$ T cells expressing CD57$^+$ in unadjusted analysis (0.175, 95% CI: 0.056 to 0.293). Furthermore, in fully adjusted models, controlling for demographic variables (including annual income, study site location, and highest level of education), height, and HIV-specific variables (including current CD4 T cell count and viral load), the association between greater BMI and both the proportion of CD28$^-$CD57$^+$ CD8$^+$ T cells and the proportion of CD28$^-$CD8$^+$ T cells expressing CD57$^+$ remained significant [0.166, (95% CI: 0.04 to 0.29) and 0.145 (0.026 to 0.263)]. The association between greater BMI and the overall proportion of CD28$^-$ CD8$^+$ cells in unadjusted (0.051, 95% CI: −0.073 to 0.175) and fully adjusted models (0.078, 95% CI: −0.053 to 0.209) were not significant.

Comparing different measures of body composition in fully adjusted models (Table 2), greater BMI and waist circumference were associated with a significantly greater proportion of CD28$^-$CD57$^+$ of CD8$^+$ T cells and the proportion of CD57$^+$ of CD28$^-$ CD8$^+$ T cells. These associations were only minimally attenuated by addition of viral load to the models, remaining significant in both cases. When examining BMI as a dichotomous variable comparing obese (BMI >30) with nonobese (BMI ≤30), there was a positive association between obesity and the proportion of CD57$^+$ of CD28$^-$CD8$^+$ T cells; however, the association was not significant (P = 0.065). Waist-to-hip ratio was not associated with significant differences in the proportion of CD28$^-$CD57$^+$ of CD8$^+$ T cells or the proportion of CD28$^-$CD8$^+$ T cells expressing CD57 regardless of adjustment for viral load (all $P > 0.01$).

In a sensitivity analyses restricted to individuals who were virologically suppressed (n = 168), the estimates for the associations of BMI and waist circumference with the CD8$^+$ phenotypes were similar to analyses with both virologically suppressed and unsuppressed participants included in the models, although the associations were no longer significant (all $P > 0.1$) (data not shown).

Association of Other Variables With CD8$^+$ Phenotypes

In fully adjusted multivariable analysis, older age was associated with a significantly greater percentage of CD8$^+$ T cells that were CD28$^-$CD57$^+$ (0.134, 95% CI: 0.009 to 0.259) and a significantly greater percentage of CD57$^+$ of CD28$^-$CD8$^+$ T cells (0.154, 95% CI: 0.037 to 0.272). Being Hispanic was also associated with a significantly greater proportion of CD57$^+$CD28$^-$CD8$^+$ T cells or CD57$^+$ of all the CD28$^-$ CD8$^+$ T cells (0.450, 95% CI: 0.069 to 0.68) in multivariable analysis.

Among the HIV-related factors, higher HIV viral load was associated with a small, albeit significant, higher percentage of CD57$^+$ CD28$^-$ of CD8$^+$ T cells (0.014, 95 CI%: 0.005 to 0.023) and percentage of CD57$^+$ of CD28$^-$CD8$^+$ T cells (0.012, 95% CI: 0.004 to 0.021) in unadjusted analyses. These associations were attenuated and ceased to be significant after adjusting for other factors. HIV viral load was not associated with a significant difference in the overall proportion of CD28$^-$ CD8$^+$ T cells in either unadjusted or fully adjusted models. Each IQR higher CD4 count was associated with a lower proportion of CD57$^+$CD28$^-$CD8$^+$ T cells (−0.241, 95% CI: −0.354 to −0.128) and CD28$^-$ CD8$^+$ T cells that were CD57$^+$ (−0.215, 95% CI: −0.324 to −0.107) and the overall proportion of CD28$^-$ CD8$^+$ T cells (−0.126, 95 CI: −0.273 to −0.047). The associations between greater CD4 count and lower

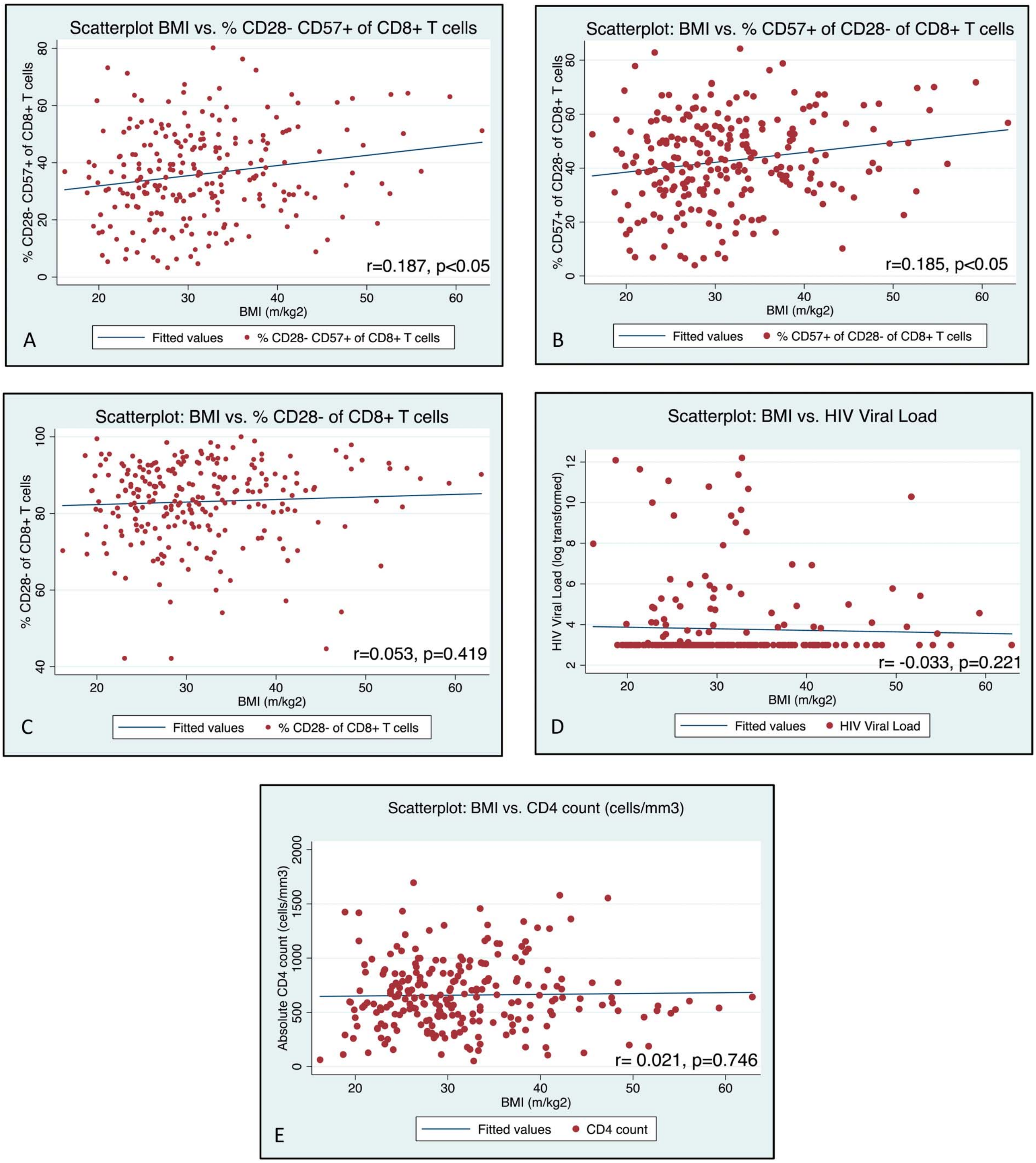

FIGURE 1. Scatterplots of BMI versus $CD8^+$ T-cell phenotypes in HIV-infected women. A, BMI versus % $CD28^-$ $CD57^+$ of $CD8^+$ T cells. B, BMI versus % $CD57^+$ of $CD28^-$ of $CD8^+$ T cells. C, BMI versus % $CD28^-$ of $CD8^+$ T cells. D, BMI versus current $CD4^+$ T cells. E, BMI versus HIV viral load.

percentage of $CD57^+CD28^-CD8^+$ T-cells count and the proportion of $CD28^-CD8^+$ T cells that were $CD57^+$ remained significant even in fully adjusted models. By contrast, each IQR higher CD4 nadir was not associated with significant differences in $CD8^+$ cell phenotypes, but longer duration on ART was associated with a significantly lower proportion of all $CD8^+$ cell phenotypes in unadjusted analysis (all $P < 0.001$). Additional exploratory analyses, adjusting for total $CD8^+$ T-cell population and $CD8^+/CD4^+$ ratio, did not did not alter the associations between 3 $CD8^+$ phenotypes and BMI. Furthermore, including percent body fat data, available for a subset of 195 women, in multivariable regression models did not alter these associations either (data not shown) (Table 3).

TABLE 2. Unadjusted and Multivariable Analysis Factors Associated With $CD8^+$ T-Cell Phenotypes in HIV-Infected Women

	% $CD28^-$ $CD57^+$ of $CD8^+$ T Cells*				% $CD57^+$ of $CD28^-$ of $CD8^+$ T Cells*	
	Unadjusted		Adjusted		Unadjusted	
	(95% CI)	P	(95% CI)	P	(95% CI)	P
Age at visit	0.104 (−0.02 to 0.228)	0.10	0.134 (0.009 to 0.259)	0.036	0.135 (0.017 to 0.253)	0.025
Annual income						
≤$30,000	Ref.		Ref.		Ref.	
$30,001+	−0.016 (−0.222 to 0.189)	0.89	0.112 (−0.121 to 0.344)	0.35	−0.016 (−0.211 to 0.179)	0.87
Site						
Bronx	Ref.		Ref.		Ref.	
Brooklyn	−0.177 (−0.507 to 0.152)	0.29	−0.111 (−0.456 to 0.234)	0.53	−0.279 (−0.592 to 0.035)	0.081
Georgetown	0.02 (−0.325 to 0.365)	0.91	0.092 (−0.28 to 0.464)	0.63	−0.126 (−0.455 to 0.203)	0.45
San Francisco	−0.18 (−0.716 to 0.355)	0.51	−0.085 (−0.629 to 0.459)	0.76	−0.409 (−0.919 to 0.101)	0.12
Chicago	−0.218 (−0.560 to 0.125)	0.21	−0.111 (−0.466 to 0.244)	0.54	−0.347 (−0.673 to −0.021)	0.037
Education						
<High school	Ref.		Ref.		Ref.	
High school degree	−0.05 (−0.295 to 0.194)	0.69	−0.039 (−0.291 to 0.212)	0.76	−0.039 (−0.271 to 0.194)	0.74
College or greater	−0.221 (−0.451 to 0.009)	0.06	−0.082 (−0.341 to 0.177)	0.53	−0.268 (−0.486 to −0.049)	0.017
Race/ethnicity						
Non-Hispanic white	Ref.		Ref.		Ref.	
Black	0.373 (0.053 to 0.693)	0.022	0.27 (−0.088 to 0.627)	0.14	0.375 (0.069 to 0.680)	0.016
Hispanic	0.408 (0.009 to 0.807)	0.045	0.453 (0.01 to 0.896)	0.045	0.45 (0.069 to 0.831)	0.021
Other	0.555 (0.014 to 1.095)	0.045	0.51 (−0.030 to 1.051)	0.064	0.507 (−0.010 to 1.023)	0.055
Body composition parameters						
BMI*	0.184 (0.06 to 0.307)	0.004	0.166 (0.040 to 0.292)	0.01	0.175 (0.056 to 0.293)	0.004
Height, cm*	0.031 (−0.103 to 0.165)	0.650	0.02 (−0.122 to 0.162)	0.78	0.019 (−0.109 to 0.147)	0.77
Waist circumference, cm*	0.139 (−0.009 to 0.287)	0.065			0.15 (0.009 to 0.290)	0.037
Hip circumference, cm*	0.177 (0.058 to 0.296)	0.004			0.165 (0.052 to 0.278)	0.005
HIV-specific parameters						
CD4 count	−0.241 (−0.354 to −0.128)	<0.001	−0.188 (−0.312 to −0.064)	0.003	−0.215 (−0.324 to −0.107)	<0.001
Viral load (log10)*	0.014 (0.005 to 0.023)	0.002	0.008 (−0.002 to 0.018)	0.10	0.012 (0.004 to 0.021)	0.006
CD4 nadir*	0.083 (−0.037 to 0.204)	0.18			0.073 (−0.042 to 0.189)	0.21
Duration of HAART*	−0.243 (−0.404 to −0.082)	0.003			−0.158 (−0.314 to −0.002)	0.047

	% $CD57^+$ of $CD28^-$ of $CD8^+$ T Cells*		% $CD28^-$ of $CD8^+$ T Cells*			
	Adjusted		Unadjusted		Adjusted	
	(95% CI)	P	(95% CI)	P	(95% CI)	P
Age at visit	0.154 (0.037 to 0.272)	0.01	−0.104 (−0.226 to 0.018)	0.094	−0.068 (−0.198 to 0.062)	0.30
Annual income						
≤$30,000	Ref.		Ref.		Ref.	
$30,001+	0.141 (−0.078 to 0.360)	0.21	−0.05 (−0.256 to 0.155)	0.63	−0.068 (−0.31 to 0.174)	0.58
Site						
Bronx	Ref.		Ref.		Ref.	
Brooklyn	−0.169 (−0.493 to 0.156)	0.31	0.307 (−0.013 to 0.628)	0.60	0.193 (−0.166 to 0.552)	0.29
Georgetown	−0.015 (−0.365 to 0.335)	0.93	0.437 (0.101 to 0.773)	0.011	0.342 (−0.045 to 0.729)	0.083
San Francisco	−0.268 (−0.78 to 0.243)	0.30	0.714 (0.193 to 1.235)	0.007	0.624 (0.058 to 1.189)	0.031
Chicago	−0.198 (−0.532 to 0.137)	0.25	0.411 (0.077 to 0.744)	0.016	0.312 (−0.058 to 0.681)	0.098
Education						
<High school	Ref.		Ref.		Ref.	
High school degree	−0.034 (−0.27 to 0.203)	0.78	−0.049 (−0.292 to 0.193)	0.69	−0.036 (−0.297 to 0.225)	0.79
College or greater	−0.155 (−0.399 to 0.089)	0.21	0.053 (−0.175 to 0.281)	0.65	0.153 (−0.117 to 0.423)	0.27
Race/ethnicity						
Non-Hispanic white	Ref.		Ref.		Ref.	
Black	0.265 (−0.071 to 0.602)	0.12	0.129 (−0.190 to 0.447)	0.43	0.128 (−0.244 to 0.499)	0.50
Hispanic	0.444 (0.027 to 0.861)	0.037	0.048 (−0.349 to 0.445)	0.81	0.19 (−0.271 to 0.650)	0.42

(*continued on next page*)

TABLE 2. (*Continued*) Unadjusted and Multivariable Analysis Factors Associated With CD8+ T-Cell Phenotypes in HIV-Infected Women

	% CD57+ of CD28− of CD8+ T Cells*		% CD28− of CD8+ T Cells*			
	Adjusted		Unadjusted		Adjusted	
	(95% CI)	P	(95% CI)	P	(95% CI)	P
Other	0.458 (−0.051 to 0.966)	0.078	0.324 (−0.215 to 0.862)	0.24	0.322 (−0.241 to 0.884)	0.26
Body composition parameters						
BMI*	0.145 (0.026 to 0.263)	0.017	0.051 (−0.073 to 0.175)	0.42	0.078 (−0.053 to 0.209)	0.24
Height, cm*	0.028 (−0.105 to 0.161)	0.68	0.037 (−0.095 to 0.169)	0.58	−0.014 (−0.161 to 0.134)	0.85
Waist circumference, cm*			−0.031 (−0.175 to 0.113)	0.67		
Hip circumference, cm*			0.062 (−0.055 to 0.179)	0.30		
HIV-specific parameters						
CD4 count	−0.17 (−0.287 to −0.054)	0.004	−0.16 (−0.273 to −0.047)	0.006	−0.126 (−0.254 to 0.003)	0.056
Viral load (log10)*	0.007 (−0.003 to 0.016)	0.16	0.011 (0.002 to 0.020)	0.021	0.006 (−0.004 to 0.017)	0.24
CD4 nadir*			0.069 (−0.050 to 0.188)	0.25		
Duration of HAART*			−0.373 (−0.528 to −0.218)	<0.001		

Data are from generalized linear regression analyses.
*Values standardized by dividing individual value by interquartile range.
HAART, highly active antiretroviral therapy.

DISCUSSION

In this population of women living with HIV infection, most of whom had been on ART for more than 10 years and were overweight or obese, we found that greater BMI was associated with a greater proportion of CD57+CD28−CD8+ T cells. We also demonstrated that, although BMI was not associated with a significant difference in the overall proportion of CD28−CD8+ T cells, greater BMI was associated with a greater proportion of CD28−CD8+ that expressed CD57 even after further adjustment for HIV viral load.

Contrary to our a priori hypothesis that adiposity promotes maturational CD8+ T cell defects that predict increased mortality in treated HIV infection (eg, a low proportion of CD28−CD8+ T cells that express CD57), we found that greater BMI was associated with greater expression of CD57 by CD28−CD8+ T cells. Furthermore, the association was only minimally attenuated by additional adjustment for HIV viral load. Given recent studies by Lee et al showing that increased expression of CD28−CD8+ T cells that express CD57 was predictive of decreased mortality in HIV-infected individuals on ART,[27,28] we speculate that the association between BMI and increased proportions of effector cells expressing CD57 may indicate that increasing BMI is immunologically protective.

In Lee's analysis, several markers of innate immune activation, including sCD14 and IL-6 were correlated with decreased CD28−CD8+ cells expressing CD57. A potential explanation for our findings of an association between greater BMI and increased CD28−CD8+ T cells expressing CD57

TABLE 3. Factors Associated With Associated With CD8+ T-Cell Phenotypes in HIV-Infected Women in (1) Multivariable Analysis Including and (2) Multivariate Analysis With Additional Adjustment for Viral Load

	% CD28− CD57+ of CD8+ T Cells				% CD57+ of CD28− of CD8+ T Cells	
	Fully Adjusted β (95% CI)	P	Fully Adjusted + Viral Load β (95% CI)	P	Fully Adjusted β (95% CI)	P
BMI*†	0.161 (0.035 to 0.287)	0.012	0.166 (0.041 to 0.292)	0.01	0.141 (0.022 to 0.259)	0.02
Waist circumference, cm*†	0.168 (0.0160 to 0.321)	0.031	0.167 (0.0148 to 0.320)	0.032	0.164 (0.0222 to 0.306)	0.024
Obesity*	0.185 (−0.012 to 0.382)	0.065	0.185 (−0.011 to 0.382)	0.065	0.151 (−0.0341 to 0.336)	0.11
Waist hip ratio, cm*†	0.0289 (−0.142 to 0.199)	0.74	0.0236 (−0.147 to 0.194)	0.79	0.0482 (−0.110 to 0.207)	0.55

	% CD57+ of CD28− of CD8+ T Cells		% CD28− of CD8+ T Cells			
	Fully Adjusted + Viral Load β (95% CI)	P	Fully Adjusted β (95% CI)	P	Fully Adjusted + Viral Load β (95% CI)	P
BMI*†	0.145 (0.026 to 0.263)	0.017	0.074 (−0.057 to 0.204)	0.27	0.0778 (−0.053 to 0.209)	0.24
Waist circumference, cm*†	0.163 (0.0210 to 0.305)	0.025	0.0162 (−0.139 to 0.171)	0.84	0.0147 (−0.141 to 0.170)	0.85
Obesity*	0.151 (−0.034 to 0.335)	0.11	0.0886 (−0.114 to 0.291)	0.39	0.0886 (−0.114 to 0.292)	0.391
Waist hip ratio, cm*†	0.0437 (−0.115 to 0.202)	0.59	−0.0864 (−0.257 to −0.0845)	0.32	−0.0907 (−0.262 to 0.081)	0.3

*Model adjusting for age, race/ethnicity, income, education, WIHS site, height, CD4 count, and viral load.
†Values standardized by dividing individual value by interquartile range.

could be that a greater BMI reflects less of an inflammation-associated catabolic state. If this were the case, it would be the converse of what is seen in HIV-uninfected elderly adults where higher frequencies of CD28^{-}CD57^{+} CD8^{+} T cells are predictive of increased mortality not improving health.[31] These contradictory results may reflect fundamentally distinct immunologic pathways mediating the functional T-cell defects that persist during treated HIV and those that characterize the aging process. Because increasing BMI in HIV-infected adults initiating ART reflects restorative changes in both lean muscle mass and adipose tissue,[32] the association between increasing expression of CD57 and BMI may be evidence of how suppressive ART leads to healthy changes in both body composition and adaptive immunity. Further research is necessary to better understand the interplay of inflammation, changing body composition, and T-cell differentiation in this population.

Another possible explanation is that increased adiposity promotes expansion of CD57^{+} cells. This seems plausible, given that persons with congenital lipoatrophy also have lower proportions of CD57^{+}CD8^{+} T cells than in the normal population.[33] Furthermore, in a study of HIV-uninfected adolescents by Spielmann et al, being at risk for obesity was associated with a higher proportion of CD28^{-}CD8^{+} T cells, including the CD57^{+}CD28^{-}CD8 subset.[34] Given that untreated HIV infection is associated with a lower proportion of CD57^{+}CD28^{-} CD8^{+} T cells, our findings suggest that some degree of adiposity may counteract the adverse changes in T-cell differentiation seen in untreated HIV infection. We found that BMI was only associated with an increase in the proportion of cells expressing CD57, rather than the larger proportion of CD28^{-}CD8^{+} T cells, which were associated with increased obesity in Spielmann's analysis. We speculate that this difference may be more consistent with a decreased immune activation (associated with a reduced catabolic state and greater BMI) in HIV allowing for greater terminal differentiation of effector CD8^{+} T cells, in contrast to a scenario where increased immune activation in obese adolescents drives CD28^{-}CD8^{+} T cells to express CD57. Nevertheless, we cannot exclude the possibility that the association between BMI and terminally differentiated CD8^{+} T cells are associated with long-term deleterious health effects. Whether uncontrolled factors, such as nutrition, food insecurity, or physical activity, mediate the association between increasing BMI and T-cell differentiation in HIV infection also remains unclear. Research in HIV-uninfected adults has shown that obesity is associated with a reduction in circulating regulatory T cells.[35] Because these cells serve to suppress immune responses and exert a suppressive function on effector T cells,[36] further research is necessary to determine whether these regulatory cells mediate the association noted in our analysis. Furthermore, whether weight loss, among obese HIV-infected women, alters T-cell differentiation warrants further exploration.

We did not find a significant association between CD57 expression and obesity when using a dichotomous variable comparing obese versus nonobese. However, the median BMI in our patient population was 30 m^{2}/kg, and 75% were overweight or obese, and therefore lack of a significant association with obesity may reflect homogeneity across the study population. Nevertheless, whether increased adipokine-mediated inflammation independently alters CD8^{+} effector T-cell populations in morbidly obese individuals is unclear. Further prospective studies may be helpful to better understand the interplay of weight gain, innate immune activation pathways, and CD8^{+} T-cell phenotypes in HIV-infected adults.

Contrary to expectation, there was an association between higher current CD4 count and a lower proportion of CD28^{-}CD8^{+} cells expressing CD57. However, higher current CD4 count was also associated with a lower proportion of CD28^{-}CD8^{+} T cells, an unexpected finding that may have been driven by unmeasured confounders. Whether other factors, such as comorbid diseases, have a confounding effect on the association is unclear and warrants further evaluation.

Our study had several limitations. We did not include an HIV-uninfected control group for comparison and cannot comment on how associations between BMI and CD8^{+} T-cell subtypes would be different in age-matched HIV-uninfected women. Furthermore, the cross-sectional design did not allow us to make conclusions on causality. Longitudinal studies relating changes in adaptive immunity to changes in body habitus are required, and such studies are currently underway. We acknowledge that BMI is an imprecise predictor that does not measure total fat mass or fat distribution, although monitoring BMI in a large sample size does provide insight into population characteristics.[37] Aerobic fitness is associated with lower age-related accumulation of terminally differentiated T cells in HIV-uninfected adults,[38] but we did not have available data on physical activity concurrent with our outcomes, and hence were unable to determine whether physical activity plays an independent role in adaptive immunity. Furthermore, we were unable to control for CMV infection, an important independent determinant of T-cell differentiation and increased CD57 expression[39] Although we expect that most study participants were CMV coinfected,[30] we have no reason to suspect that CMV serostatus would have confounded the association of BMI with CD57 expression found in our analysis.

There were also many advantages to our study. We were able to conduct this work with ethnically diverse HIV-infected women in the United States. Research is fundamentally lacking in this group, and research in a wide variety of settings will only improve our understanding of how ART alters adaptive immunity. The population was restricted to women, on ART who mostly had suppressed viral loads, and excluded women with concomitant viral hepatitis, autoimmune disease and/or cancer—such restrictions reduced concerns about confounding from gender, comorbid illness, or differential treatment—that might independently influence inflammation and T-cell differentiation. The cohort size for this particular study, with immunological parameters measured on each participant, was relatively large, much more so than work that has been previously done. Furthermore, it included woman, most of whom had been on ART for many years. Finally, our work is largely consistent with an evolving body of literature regarding the role of CD28^{-}CD8^{+} T cells in HIV immunology.

In conclusion, in a relatively large cohort of HIV-infected women on ART, we found that greater BMI is associated with greater expression of CD57 on the proportion of $CD28^-CD8^+$ T cells, and increase in the proportion of $CD57^+CD28^-CD8^+$ T cells, but not an accumulation of the overall $CD28^-CD8^+$ T-cell subset. The impact of body composition on $CD8^+$ T-cell phenotype is complex in the setting of HIV infection, given known effects of HIV on lean mass and subcutaneous tissue. Future research is needed using careful assessment of the various body composition compartments to understand the prognostic importance of these associations on clinical outcomes in HIV-infected individuals.

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