CLINICAL AND VACCINE IMMUNOLOGY, June 2011, p. 940–946 Vol. 18, No. 6
1556-6811/11/$12.00 doi:10.1128/CVI.00020-11

Impact of Weight on Immune Cell Counts among HIV-Infected Persons▽

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Received 18 January 2011/Returned for modification 6 March 2011/Accepted 16 April 2011

Prior studies have shown that weight may impact immune cell counts. However, few data exist about the relationship of weight and immune cell counts among HIV-infected patients. We examined documented HIV seroconverters (mean window, 15.7 months) in a prospective U.S. Military HIV Natural History Study (1 January 1986 to 20 January 2010). We estimated the association of the time-updated body mass index (BMI) category with changes in immune cell counts from HIV diagnosis across time (mean follow-up of 5.1 years) using multiply adjusted longitudinal linear mixed-effects models. Of 1,097 HIV seroconverters, 448 (41%) were overweight and 93 (8%) were obese at HIV diagnosis. Immune cell counts at HIV diagnosis did not significantly differ by BMI category. In the longitudinal models for those diagnosed before the advent of the highly active antiretroviral therapy (HAART) era, mean postdiagnosis decreases in the white cell count, total lymphocyte count, CD4 count, CD4 percentage, and CD4/CD8 ratio were less as the BMI category increased (all with *P* values of <0.05). Among HIV seroconverters diagnosed in the HAART era, obese compared to normal-weight patients had significantly smaller increases in CD4 counts, CD4 percentages, and the CD4/CD8 ratio (all with *P* values of <0.05). Similar findings were also noted among underweight versus normal-weight patients. In conclusion, although BMI was not associated with immune cell levels at the time of HIV diagnosis, weight appears to affect immune cells counts over the course of infection. In the HAART era, being either underweight or obese was associated with smaller increases in several important immune cell levels, including the CD4/CD8 ratio.

As HIV-infected persons are experiencing longer life expectancies during the highly active antiretroviral therapy (HAART) era, the prevalence of being overweight or obese among this population is rising (2, 6, 18, 27, 38). Excess weight contributes to several health-related complications, including hypertension, diabetes, cardiovascular disease, kidney disease, cancers, and excess mortality (5, 13, 14, 35, 42, 46). It is possible that excess weight may also have a negative effect on immune cell counts.

The impact of weight on immune cells, to date, has largely been evaluated among HIV-uninfected persons, with variable results, some suggesting that being overweight or obese is associated with higher immune cell levels (28, 31, 47) and others showing that obesity results in decreased immune counts and function (24, 25, 39, 40). It is known that obesity is associated with higher rates of infectious complications, severity of certain viral infections (e.g., 2009 H1N1 influenza A and hepatitis C virus), and poorer vaccine responses (8, 10–12, 19, 21, 32, 36, 41, 48), supporting its potential detrimental effects on immune responses.

The impact of weight on immune cell levels among HIV-infected persons during the HAART era remains largely unknown. A small study noted that obese HIV patients had higher CD3, CD8, and total lymphocytes counts but had similar CD4 cell counts, compared to normal-weight persons (1). However, this study was limited by its lack of data on HIV duration, cross-sectional design, and a population consisting only of diabetic patients. Recently, we reported that obese patients gained fewer CD4 cells after HAART initiation, suggesting a potential detrimental immune response associated with excess weight (7). In the current study, we investigated the relationship between body weight and a variety of immune cell counts at diagnosis and over the course of HIV infection among a cohort of documented HIV seroconverters who had serial immune cell measurements and longitudinal weight data.

MATERIALS AND METHODS

We examined HIV participants of the U.S. Military HIV Natural History Study (NHS) during 1 January 1986 to 20 January 2010. NHS participants were military beneficiaries (active duty, retirees, and dependents) who received care at one of seven U.S. geographic locations, as previously described (44). Medical care for beneficiaries, including antiretroviral medications, is free of charge. Active-duty members are HIV negative upon service entry and undergo mandatory testing every 1 to 5 years. NHS participants are evaluated on a biannual basis, and data including weight measurements, laboratory measurements, and medications are collected utilizing standardized collection procedures.

Participants in this substudy included those with a documented HIV seroconversion window of ≤3 years, those without antiretroviral use prior to the baseline CD4 cell count, those for which the CD4 count was available, and those with baseline BMI measures between −30 and 183 days from the time of an HIV-

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▽ Published ahead of print on 27 April 2011.

TABLE 1. Baseline[a] study population characteristics among HIV seroconverters

Factor[b]	Value for BMI group[c]					*P* value[d]
	Total cohort	Underweight	Normal	Overweight	Obese	
BMI, kg/m^2	25.2 (3.5)	17.4 (1.1)	22.6 (1.6)	26.9 (1.4)	32.6 (2.1)	
Demographics						
Age, yr	28.9 (6.8)	24.7 (4.4)	27.9 (6.7)	29.9 (6.9)	31.0 (6.8)	<0.001
No. (%) male	1,053 (96)	9 (69)	522 (96)	434 (97)	88 (95)	<0.001
Ethnicity [no. (%)]						0.02
White/non-Hispanic	487 (44)	7 (54)	264 (49)	186 (42)	30 (32)	
African American	439 (40)	5 (38)	207 (38)	182 (41)	45 (48)	
Hispanic/Latino	107 (10)	1 (8)	37 (7)	56 (12)	13 (14)	
Other	64 (6)	0 (0)	35 (6)	24 (5)	5 (5)	
HIV-related factors						
Seroconversion window, yr	1.3 (0.7)	1.2 (0.8)	1.3 (0.7)	1.3 (0.7)	1.4 (0.7)	0.83
No. (%) with HIV diagnosis in HAART era	700 (64)	7 (54)	308 (57)	309 (69)	76 (82)	<0.001
Baseline HIV-RNA, copies/ml [no. (%)]						<0.001
Missing	229 (21)	3 (1)	143 (26)	75 (17)	8 (9)	
<1,000	88 (8)	1 (8)	36 (7)	42 (9)	9 (10)	
1,000-10,000	200 (18)	0 (0.0)	89 (16)	91 (20)	20 (22)	
10,000-100,000	435 (40)	6 (46)	194 (36)	185 (41)	50 (54)	
≥100,000	145 (13)	3 (23)	81 (15)	55 (12)	6 (6)	
Time to first CD4 count, days	37.1 (25.9)	23.5 (18.9)	37.2 (27.3)	37.2 (24.9)	37.6 (23.1)	0.30
No. of immune cell counts available (out of 8), median (IQR[e])	7 (7–7)	7 (7–7)	7 (7–7)	7 (7–7)	7 (7–7)	

[a] Baseline is within −30 to +183 days of the documented HIV-positive date.
[b] Values are represented as mean (standard deviation) for continuous values and number (percentages) for categorical variables unless otherwise stated.
[c] Cohort sizes were as follows: total, $n = 1,097$; underweight, $n = 13$; normal, $n = 543$; overweight, $n = 448$; obese, $n = 93$.
[d] *P* value calculated from analysis of variance for continuous variables or chi-square test for categorical variables.
[e] IQR, interquartile range.

positive test result and with repeated measurements during at least one follow-up visit. A total of 1,097 NHS participants were included in this substudy; the main reason for exclusion was not having a narrow seroconverting window (≤3 years) or unavailability of baseline BMI or CD4 measure.

Data collected for this analysis at HIV diagnosis (baseline) included the following: weight measured by a calibrated scale, height, demographics (age, gender, self-reported ethnicity), seroconversion window between the last HIV-negative and first HIV-positive dates, immune cell counts, which were drawn as part of clinical care and included the white blood cell count, total lymphocyte count, and T-cell subset panel (CD4 count and percentage, CD8 count and percentage, CD4/CD8 ratio, CD3 percentage, CD19 percentage, and CD56 percentage by flow cytometry), time to first CD4 count, and HIV RNA level (Roche Amplicor). Data collected at each follow-up visit included weight, immune cell counts, and antiretroviral therapy prescription dates.

The study period was *a priori* divided into pre-HAART (1986 to 1995) and HAART (1996 to 2010) periods. Weight was categorized by body mass index (BMI) (kg/m^2) as <18.5 kg/m^2 (underweight), 18.5 to 24.9 kg/m^2 (normal weight), 25 to 29.9 kg/m^2 (overweight), and ≥30 kg/m^2 (obese) (29, 49). Our study was approved by the governing Institutional Review Board, and participants provided written informed consent.

Immune cell counts at HIV diagnosis were compared across BMI categories using an *F* test. Adjusted models were performed and adjusted for variables that could affect immune cell counts over time, including age, gender, ethnicity, length of seroconversion window, baseline HIV RNA level, and era of HIV diagnosis (pre- and post-HAART). In subgroup analyses, differential BMI effects between eras of HIV diagnosis were assessed through tests for interaction between BMI category and era of diagnosis.

Change in the immune cell counts from HIV diagnosis over time was computed at each follow-up visit. Using longitudinal linear mixed-effects models with a random intercept for each participant, regressions for change in each immune cell count were fitted using all follow-up data. Models were adjusted for age, gender, ethnicity, length of seroconversion window, follow-up visit, immune cell count, and HIV RNA level at HIV diagnosis, cumulative time on mono- or dual-antiretroviral therapy, cumulative time on HAART, and time-updated BMI category. Time-updated BMI utilized the BMI measurement obtained at each follow-up visit. Cumulative time on antiretroviral therapy (ART) was calculated from HIV diagnosis to the date of each immune cell measurement.

Models were performed separately among participants with an HIV diagnosis date that occurred in the pre-HAART era and those with an HIV diagnosis date that occurred in the HAART era. Missing weight values were not imputed. Results were considered statistically significant for *P* values of <0.05. All analyses were conducted using the SAS software program (version 9.1; SAS Institute, Cary, NC).

RESULTS

Study population. Of 1,097 HIV seroconverters, 543 (50%) were of normal weight, 448 (41%) were overweight, 93 (8%) were obese, and 13 (1%) were underweight at HIV diagnosis (Table 1). The mean age of our study cohort was 29 years, 96% were male, and ethnicity included 44% Caucasian, 40% African American, 10% Hispanic, and 6% other. Sixty-four percent of our cohort was diagnosed in the HAART era. The mean seroconversion window was 15.7 months (standard deviation [SD], 8.6), and the mean time to first CD4 count was 37 days (SD, 26).

At HIV diagnosis, the mean overall CD4 count was 538 (SD, 246) cells/mm^3 and the HIV RNA level was <1,000 copies/ml for 8%, 1,000 to 10,000 for 18%, 10,000 to 100,000 for 40%, and >100,000 for 13%; 21% had missing RNA levels, mostly due to unavailability of viral load testing prior to 1996. Demographic characteristics differed by weight category: those who were underweight were younger and more likely to be female, while those who were obese were more likely to be of a non-Caucasian ethnicity and to have HIV diagnosed in the HAART era (all with *P* values of <0.01). There were no differences by weight category for the seroconversion window or time to first CD4 count.

TABLE 2. Immune cell counts by BMI categories at HIV diagnosis

Immune count type[a]	Value for BMI group[b]					Unadjusted *P* value[c]	Adjusted *P* value[c,d]
	Overall	Underweight	Normal	Overweight	Obese		
White blood cell count							
% available	79	85	83	76	69		
Mean ± SD	5,462 ± 1662	5,673 ± 2182	5,522 ± 1,729	5,414 ± 1,596	5,263 ± 1434	0.58	0.97
Lymphocyte count							
% available	77	85	82	74	68		
Mean ± SD	2,036 ± 863	2,154 ± 1448	2,091 ± 1,005	1,982 ± 651	1,913 ± 572	0.21	0.48
CD4 count							
% available	100	100	100	100	100		
Mean ± SD	538 ± 246	497 ± 253	538 ± 246	545 ± 252	513 ± 219	0.64	0.54
CD4 percentage							
% available	100	100	100	100	100		
Mean ± SD	27 ± 9	25 ± 12	27 ± 9	28 ± 8	26 ± 9	0.09	0.08
CD8 count							
% available	100	100	100	100	100		
Mean ± SD	989 ± 631	1,329 ± 1191	1,038 ± 778	927 ± 396	952 ± 432	**0.009**	0.05
CD8 percentage							
% available	100	100	100	100	100		
Mean ± SD	48 ± 11	52 ± 15	49 ± 11	47 ± 10	47 ± 12	**0.03**	0.06
CD4/CD8 ratio							
% available	100	100	100	100	100		
Mean ± SD	0.6 ± 0.3	0.6 ± 0.3	0.6 ± 0.3	0.7 ± 0.3	0.6 ± 0.4	0.10	0.10
CD3 percentage							
% available	91	92	87	94	97		
Mean ± SD	78 ± 7	78 ± 7	78 ± 8	77 ± 7	76 ± 8	0.12	0.24
CD19 percentage							
% available	85	85	80	88	92		
Mean ± SD	10 ± 5	12 ± 7	10 ± 5	11 ± 5	11 ± 5	0.25	0.22
CD56 percentage							
% available	88	92	83	92	97		
Mean ± SD	10 ± 6	10 ± 4	10 ± 6	10 ± 6	11 ± 6	0.85	0.79

[a] % available, percentage for each group with measurement available within −30 to +183 days of documented HIV-positive date for each immune cell type.
[b] Cohort sizes were as follows: overall, $n = 1,097$; underweight, $n = 13$; normal, $n = 543$; overweight, $n = 448$; obese, $n = 93$.
[c] *P* values obtained from an *F* test which tests if the means of the BMI categories are equal. Boldface values are *P* values of <0.05.
[d] Model adjusted for age, gender ethnicity, length of seroconversion window, baseline HIV RNA level, and era of HIV diagnosis.

Immune cells by weight category at HIV diagnosis. We examined immune cell levels at HIV diagnosis across the four weight categories across both eras of the epidemic (Table 2). Mean CD4 counts at HIV diagnosis were 497, 538, 545, and 513 cells/mm^3 for underweight, normal, overweight, and obese patients, respectively, and were not significantly different in the unadjusted ($P = 0.64$) or adjusted ($P = 0.54$) models. We also examined the white blood cell count, total lymphocyte count, CD3, CD19, and CD56 percentages, and the CD4/CD8 count ratio and found no significant differences between the weight categories. The only immune cell type that differed by weight category at HIV diagnosis was the CD8 count and percentage, which were highest among underweight HIV-infected persons, but these findings were no longer statistically significant in the adjusted models.

We also examined the baseline immune cell values by HAART era (pre- versus post-HAART) and found similar overall trends. Additionally, among those diagnosed with HIV in the HAART era, the CD4 percentage appeared to have a reverse U-shaped distribution among the respective weight categories: 21%, 26%, 28%, and 25% ($P = 0.02$). In the pre-HAART era, the CD19 percentage was noted to increase across the weight categories (7%, 10%, 11%, and 14%; $P = 0.004$), but categories were not significantly different in the HAART era (14%, 10%, 10%, and 10%; $P = 0.33$), resulting in a significant category-by-era interaction ($P = 0.009$) (data not shown).

Changes in immune cell counts by weight category during HIV infection. We estimated the associations of time-updated BMI category with changes in immune cell counts from HIV diagnosis across time (mean follow-up of 5.1 years) using multiply adjusted longitudinal linear mixed-effects models (Table 3). We examined the data stratified by the HAART era (pre- versus post-HAART), since several characteristics varied by era: those in the HAART era were more likely to be obese, older, or Hispanic or of other ethnicities, had a shorter sero-

TABLE 3. Multiply adjusted models[a] for association between time-updated BMI category and change in immune cell counts among HIV-infected persons diagnosed in the pre-HAART and HAART eras

Measurement and BMI category	Value by treatment era					
	Pre-HAART era			HAART era		
	Estimated mean change[b]	Estimated difference[c] (SE)	*P* value[d]	Estimated mean change[b]	Estimated difference[c] (SE)	*P* value[d]
WBC[e]						
BMI category (time updated)						
Underweight	−1,068	−478 (302)	0.11	−233	−326 (357)	0.36
Normal	−590	Referent		93	Referent	
Overweight	−458	132 (76)	0.08	81	−11 (77)	0.88
Obese	−316	274 (134)	**0.04**	75	−18 (116)	0.88
Lymphocyte count						
BMI category (time updated)						
Underweight	−452	−171 (128)	0.18	−233	−276 (160)	0.08
Normal	−281	Referent		43	Referent	
Overweight	−191	90 (32)	**0.005**	59	16 (35)	0.64
Obese	−118	164 (57)	**0.004**	34	−9 (53)	0.86
CD4 cell count						
BMI category (time updated)						
Underweight	−161	−35 (39)	0.37	5	−94 (35)	**0.007**
Normal	−126	Referent		99	Referent	
Overweight	−94	32 (11)	**0.003**	111	12 (9)	0.16
Obese	−49	77 (19)	**<0.001**	71	−28 (13)	**0.03**
CD4 percentage						
BMI category (time updated)						
Underweight	−10.5	−6.3 (1.3)	**<0.001**	1.1	−3.1 (1.1)	**0.004**
Normal	−4.3	Referent		4.2	Referent	
Overweight	−2.9	1.3 (0.4)	**<0.001**	3.8	−0.4 (0.3)	0.18
Obese	−2.1	2.2 (0.7)	**<0.001**	2.8	−1.3 (0.4)	**<0.001**
CD8 count						
BMI category (time updated)						
Underweight	−30	54 (72)	0.45	−50	13 (60)	0.83
Normal	−84	Referent		−63	Referent	
Overweight	−48	37 (20)	0.06	−12	51 (15)	**<0.001**
Obese	−26	59 (35)	0.09	−36	27 (22)	0.23
CD8 percentage						
BMI category (time updated)						
Underweight	10.0	7.1 (1.5)	**<0.001**	−2.2	2.0 (1.3)	0.13
Normal	2.9	Referent		−4.3	Referent	
Overweight	3.0	0.1 (0.4)	0.86	−3.4	0.8 (0.3)	**0.01**
Obese	2.9	−0.0 (0.8)	0.97	−3.1	1.1 (0.5)	**0.03**
CD4/CD8 ratio						
BMI category (time updated)						
Underweight	−0.27	−0.16 (0.05)	**<0.001**	0.08	−0.10 (0.05)	**0.04**
Normal	−0.10	Referent		0.18	Referent	
Overweight	−0.09	0.01 (0.01)	0.26	0.16	−0.02 (0.01)	0.06
Obese	−0.04	0.06 (0.02)	**0.008**	0.12	−0.06 (0.02)	**<0.001**
CD3 percentage						
BMI category (time updated)						
Underweight	2.3	1.8 (1.5)	0.22	−1.7	−1.3 (1.0)	0.19
Normal	0.5	Referent		−0.4	Referent	
Overweight	1.2	0.8 (0.4)	**0.03**	−0.3	0.1 (0.3)	0.79
Obese	2.5	2.1 (0.6)	**<0.001**	−0.8	−0.5 (0.4)	0.22
CD19 percentage						
BMI category (time updated)						
Underweight	−0.9	−2.1 (1.2)	0.07	2.5	1.4 (0.7)	0.06
Normal	1.2	Referent		1.1	Referent	
Overweight	0.5	−0.6 (0.3)	**0.02**	1.0	−0.1 (0.2)	0.50
Obese	0.1	−1.1 (0.5)	**0.02**	0.9	−0.1 (0.3)	0.59

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TABLE 3—*Continued*

Measurement and BMI category	Value by treatment era					
	Pre-HAART era			HAART era		
	Estimated mean change[b]	Estimated difference[c] (SE)	*P* value[d]	Estimated mean change[b]	Estimated difference[c] (SE)	*P* value[d]
CD56 percentage						
BMI category (time updated)						
Underweight	−1.9	1.2 (1.0)	0.24	−0.1	0.8 (0.9)	0.37
Normal	−3.1	Referent		−0.9	Referent	
Overweight	−3.3	−0.2 (0.3)	0.40	−0.7	0.3 (0.2)	0.20
Obese	−3.1	−0.0 (0.5)	0.98	−0.1	0.9 (0.3)	**0.005**

[a] Models adjusted for age, gender, ethnicity, follow-up visit, length of seroconversion window, baseline immune cell counts or percentages, baseline HIV RNA level, time-updated years on non-HAART ART, and time-updated years on HAART.

[b] Change in immune cell count or percentage, averaged across all visits. For example, among participants with a normal BMI diagnosed in the HAART era, the CD4 count increased on average by 99 cells/mm^3.

[c] Average change in immune cell count or percentage for a BMI category (underweight, overweight, or obese) compared to the normal-BMI category. For example, CD4 counts for obese participants diagnosed in the HAART era increased on average 71 cells/mm^3; the estimated difference compared to the group with normal BMI is 71 − 99 = −28.

[d] Tests if the mean changes in immune cell count or percentage between BMI category (underweight, overweight, or obese) and the normal BMI category are significantly different from each other. For example, obese participants diagnosed in the HAART era compared to those with normal weight had significantly different increases in CD4 count (+71 versus +99 cells/mm^3; $P = 0.03$). Boldface values are *P* values of <0.05.

[e] WBC, white blood cell.

conversion window, were less likely to have a missing HIV RNA level, and had lower CD4 cell counts at diagnosis (all *P* values of <0.001).

In the multiply adjusted longitudinal models for those diagnosed in the pre-HAART era ($n = 397$; mean follow-up of 6.5 years), the mean postdiagnosis decreases in the white blood cell count were less as the BMI category increased: −1,068, −590, −458, and −316 cells/mm^3, respectively ($P < 0.001$) (Table 3). Compared to normal-weight persons, those who were obese ($P = 0.04$) had smaller reductions in the white blood cell counts over time, with similar trends for those who were overweight ($P = 0.08$). Similar findings were noted for the total lymphocyte count. Regarding the CD4/CD8 ratio, compared to normal-weight persons (−0.10), those who were obese (−0.04; $P < 0.008$) had smaller reductions over time, while those who were underweight had larger reductions (−0.27; $P < 0.001$). The CD4 count and percentages had similar findings. Finally, obese patients had larger increases in CD3 percentages and smaller increases in CD19 percentages than normal-weight persons. We repeated all analyses, censoring at HAART start among those surviving into the HAART era, and found similar results, although findings for CD3 and CD19 were no longer present (data not shown).

Among patients diagnosed in the HAART era ($n = 700$; mean follow-up of 4.2 years), the mean postdiagnosis changes in the white blood cell and total lymphocyte counts were not significantly different over time by BMI category (Table 3). The mean changes in CD4 counts over time were +5, +99, +111, and +71 cells/mm^3, respectively ($P < 0.001$). Consistent with our previous work (7), obese HIV-infected persons, compared to those with normal weight, had significantly smaller increases in the CD4 count (+71 versus +99 cells/mm^3; $P = 0.03$). HIV patients who were underweight, compared to those with normal weight, also had poorer CD4 increases over time (+5 versus +99 cells/mm^3; $P = 0.007$). The change in CD4 percentage showed similar trends for obese versus normal-weight persons (+3% versus +4%; $P < 0.001$) and underweight compared to normal-weight persons (+1% versus +4%; $P = 0.004$). The mean changes in CD8 counts across the BMI categories were −50, −63, −12, and −36 cells/mm^3; overweight and obese patients experienced less reduction in the CD8 counts during the HAART era, although only the former finding was statistically significant ($P < 0.001$). Regarding the CD8 percentage, both obese and overweight persons had significantly less reduction in the CD8 percentages than normal-weight persons. Finally, the increase in the CD4/CD8 ratio was smaller over time for obese patients than for normal-weight persons (0.12 versus 0.18; $P < 0.001$). A sensitivity analysis of all models was conducted, censoring at HAART initiation, with similar, although attenuated, results, likely due to the reduced follow-up time.

DISCUSSION

Since the advent of HAART, the prevalence of obesity has increased among HIV-infected persons (2, 6, 18, 27, 38), similar to trends noted in the general population (35). Excess weight has been associated with several adverse medical conditions (5, 13, 14, 42, 46), but its potential effects on immune cell counts remain unclear, with some studies in the general population showing obesity is associated with higher immune cell counts (28, 31, 47), while others show no relationship or reduced immune function (24, 25, 39, 40). Understanding the potential impact of weight changes on immune cells may be particularly important among HIV-infected persons, since this population is already susceptible to virus-induced immunosuppression.

Our study demonstrated that although the baseline weight categories did not significantly impact immune cell counts at the time of diagnosis among documented HIV seroconverters, weight appeared to affect immune cell counts over the course of HIV infection. Our finding that weight was not significantly related to the immune cell counts at HIV diagnosis was expected. Since we evaluated documented HIV seroconverters with narrow windows (≤3 years), it was unlikely that weight would affect the immune cell levels during this short time

interval. Only one other study evaluated the impact of weight on a variety of immune cell levels, but that population had unknown dates of HIV infection, limiting the ability to make direct associations (1).

In our longitudinal models, we noted associations between time-updated weight categories and several immune cell counts, which varied with the availability of HAART. During the pre-HAART era, obese HIV patients had less reduction in their white blood cell counts, total lymphocyte counts, CD4 counts, CD4 percentages, and CD4/CD8 ratio during the course of HIV infection. The apparent benefit of excess weight among HIV-infected persons was likely the result of nutritional stores helping preserve immune levels in the setting of AIDS-related conditions. For example, during this era, weight loss was often an ominous sign of impending events, such as opportunistic infections and death (9, 34, 45). Our findings are concurrent with those in prior reports which noted that higher BMIs were associated with higher CD4 counts and improved survival (37, 38).

Since the advent of HAART, the incidence of wasting has declined, and now patients are often overweight or obese (6, 18, 26, 27). Studies during the early HAART era found that underweight persons continued to have an increased risk of HIV progression, but researchers did not report a differential impact on CD4 counts among obese compared to normal-weight patients (20, 38). Studies in developing countries have shown that obesity is associated with a lower risk of AIDS-defining events, including tuberculosis and death (17). We evaluated the impact of weight on postdiagnosis immune cell levels among HIV patients diagnosed in the HAART era with open access to antiretroviral medications. We noted that underweight persons continued to have reduced levels of vital immune cells, as described during the pre-HAART era. We also found that obese patients, compared to normal-weight patients, had smaller increases in the CD4/CD8 ratio, CD4 cell counts, and percentages, as well as less reduction in CD8 percentages. Of note, these changes occurred without concurrent changes in the white blood or total lymphocyte counts, suggesting that weight may adversely affect specific components of the cellular immune system.

The pathophysiology of these adverse immune effects was not specifically evaluated in our study and requires further investigation. Since our sensitivity analyses identified similar patterns of altered immune cell levels among obese versus normal-weight persons before the receipt of HAART, it is unlikely that these findings were due solely to differing antiretroviral efficacy by weight. Obese patients have heightened levels of C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α) compared to normal-weight persons in the general population (3, 15, 27, 43). BMI is associated with increased inflammation in HIV-infected individuals, as evidenced by increased CRP, even in the setting of HAART (4), and systemic inflammation has been linked to HIV progression (16). The inflammatory state associated with obesity may therefore lead to increased destruction and poorer immune cell recovery among HIV-infected persons. Additionally, obesity often leads to increased levels of leptin and reduced adiponectin production, creating a proinflammatory state which may affect T cell number and function (22, 23, 30, 39–41).

Regarding the clinical significance of our findings, we found that over a mean follow-up of 4.2 years, HIV-infected persons in the HAART era who were obese had 28 fewer CD4 cells than those who had a normal weight, and underweight patients had 94 fewer CD4 cells than normal-weight patients. If cell changes by BMI category continued to aggregate in a similar pattern over a longer follow-up period, we could see approximately 100 CD4 cell differences between obese and normal-weight patients over 15 years and between underweight and normal-weight patients over only 5 years. Of note, a change in the CD4 count of 100 cells/mm^3 is of clinical significance and suggests HIV disease progression and a heightened risk of HIV-related diseases. Furthermore, it is possible that obesity may have additional adverse effects on immune cell functioning (10, 11, 19, 21, 32, 36, 41, 48) not measured in our study.

As HIV-infected persons are living longer, non-AIDS-defining comorbidities, such as cardiovascular disease and malignancies, are now important causes of morbidity and mortality (33). Since excess weight contributes to the development of these disorders, obesity should be considered an important health issue among HIV-infected persons. Together, these data suggest that weight management programs may be important components of HIV care.

Limitations of our study include the lack of data on immune function. Although the number of immune cells and percentages were associated with weight, we did not evaluate the functionality of these cells. Despite our longitudinal analyses, we could not establish a causative relationship between increased weight and alterations in immune cell counts. Although it is unlikely that changes in immune cell counts would lead to obesity, the direction of this relationship requires more investigation. We did not evaluate all NHS participants in this analysis; however, the main reason was to focus on documented seroconverters. Finally, we acknowledge that the majority of our participants were male; hence, the findings may not be generalizable to women. Furthermore, since we evaluated a cohort of patients with free access to medical care during the HAART era, our findings may not be applicable to patients with limited nutritional and medical resources.

Strengths of our study included our evaluation of documented HIV seroconverters. Prior studies have examined HIV patients at various stages of infection and were not able to control for length of HIV infection; consequently, temporal relationships between weight changes and immune cell counts were less precise. In addition, our study population had serial immune cell measurements and weight data during the course of their HIV infection. Furthermore, our evaluation of weight and immune cell changes is the largest study to date and spanned both the pre- and post-HAART eras.

In summary, during the HAART era, being either underweight or obese was associated with smaller increases in several important immune counts. These data suggest that HIV providers should carefully monitor their patients' weights with the goal of obtaining and maintaining normal weights among HIV-infected persons.

ACKNOWLEDGMENTS

The Infectious Disease Clinical Research Program HIV Working Group is comprised of Susan Banks, Mary Bavaro, Helen Chun, Cathy

Decker, Conner Eggleston, Susan Fraser, Heather Hairston, Josh Hartzell, Arthur Johnson, Michael Landrum, Alan Lifson, Michelle Linfesty, Grace Macalino, Jason Maguire, Scott Merritt, Robert O'Connell, Jason Okulicz, Sheila Peel, John Powers, Timothy Whitman, Glenn Wortmann, and Michael Zapor.

Support for this work (IDCRP-000-06) was provided by the Infectious Disease Clinical Research Program (IDCRP), a Department of Defense (DoD) program executed through the Uniformed Services University of the Health Sciences. This project has been funded in whole or in part with federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), under Inter-Agency Agreement Y1-AI-5072.

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