

Weight Loss as a Predictor of Survival and Disease Progression in HIV Infection

*David A. Wheeler, †Cynthia L. Gibert, ‡Cynthia A. Launer, §Norma Muurahainen,
†Richard A. Elion, ||Donald I. Abrams, ‡Glenn E. Bartsch, and the Terry Beirn Community
Programs for Clinical Research on AIDS

*Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland; †Washington Regional AIDS
Program, Veterans Affairs Medical Center, Washington, D.C.; ‡Terry Beirn Community Program for Clinical Research on AIDS
Statistical Center, Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, Minnesota;
§Philadelphia FIGHT, Philadelphia, Pennsylvania; and ||Community Consortium, San Francisco, California, U.S.A.

Summary: Severe weight loss in HIV is associated with decreased length of survival. It is unclear whether mild weight loss is associated with an increased risk of death or opportunistic complications of HIV. Participants in four interventional studies ($n = 2382$) conducted by a community-based clinical trials network were evaluated for percentage change in weight during their first 4 months in the study. Proportional hazards models were performed for the occurrence of opportunistic complications and death subsequent to the 4-month visit. The relative risk of death and opportunistic complications for those with 5% to 10% weight loss over 4 months was 2.22 ($p < .001$) and 1.89 ($p < .001$), respectively, and 1.26 ($p < .01$) and 1.19 ($p < .01$) among those who lost 0% to 5% of their body weight, respectively, when compared with those with no weight loss. Among those who lost 5% to 10% of their body weight, the relative risk of individual opportunistic complications increased significantly, including *Pneumocystis carinii* pneumonia (PCP) (1.61; $p < .01$), cytomegalovirus (CMV) (2.33; $p < .001$), and *Mycobacterium avium* complex (MAC) (1.81; $p < .01$). As little as 5% weight loss over a 4-month period is associated with increased risk of death and opportunistic complications in HIV. A weight loss of 5% to 10% is also associated with an increased risk of individual opportunistic complications. **Key Words:** HIV—Wasting—Weight loss—Survival—Opportunistic infection.

The wasting syndrome has become increasingly recognized in adults infected with HIV in the United States (1,2) and at present accounts for approximately 18% of initial AIDS-defining conditions (3). Weight loss, with or without associated symptoms, has been described in many people with advanced HIV infection (4-6), particularly in the setting of acute opportunistic infection or gastrointestinal disease (7,8). Early studies of body composition in men with late stage disease demonstrated a

relation between the degree of weight loss and time to death (9). Epidemiologic studies in gay men have suggested a relation between severe weight loss preceding an AIDS diagnosis and survival following AIDS (10).

Although severe weight loss (>10% of body weight) has been associated with decreased survival, it is unclear whether smaller degrees of weight loss are predictive of early death. Data are also insufficient to extrapolate these findings in gay white men, to populations that include women, injection drug users, and minorities. Furthermore, although weight loss is seen in the setting of acute opportunistic infections, no evidence suggests that weight loss itself is predictive of an increased risk of subsequent opportunistic complications.

Address correspondence and reprint requests to David A. Wheeler, 3289 Woodburn Road, Suite 200, Annandale, Virginia 22003 U. S. A.

David A. Wheeler is currently affiliated with Infectious Diseases Physicians, Inc., Annandale, Virginia, U.S.A.

Manuscript received August 4, 1997; accepted December 23, 1997.

To determine whether mild (0%–5%) or moderate (5%–10%) weight loss is predictive of decreased survival and to examine whether a relation exists between weight loss and the subsequent development of opportunistic complications in a heterogeneous group of HIV-infected adults, we analyzed data from a large community-based research network.

METHODS

Patients and Data Collection

A community-based cohort of HIV-infected adults was identified, which included all participants with <500 CD4 cells/mm³, who had enrolled in one of four previously reported, interventional trials conducted between September 1990 and August 1995 within the NIH-funded Terry Bein Community Program for Clinical Research on AIDS (CPCRA). These included an evaluation of pyrimethamine for prophylaxis of toxoplasmic encephalitis (11), didanosine versus zalcitabine in advanced HIV infection (12), combination therapy versus nucleoside analogue monotherapy (13), and oral ganciclovir for cytomegalovirus (CMV) prophylaxis (14). These four clinical-endpoint studies were selected from the CPCRA cross-protocol database because they included bimonthly follow-up visits, in which data regarding weight, vital status, and progression of HIV disease were collected. Participants were enrolled at one of 17 units nationwide. In addition to body weight, baseline data included age, race, gender, HIV risk behavior (history of injection drug use, men who have sex with men), CD4 cell count, hemoglobin, antiretroviral use, and use of *Pneumocystis carinii* pneumonia (PCP) prophylaxis. Four-month data included body

weight and documentation of any opportunistic complications since the baseline visit. Percentage weight change was defined as (4-month weight – baseline weight)/(baseline weight × 100). Data from all subsequent study visits were analyzed for the occurrence of any opportunistic complications or death following the 4-month visit.

Statistical Analysis

The primary outcomes of interest were percentage weight change during a 4-month period following randomization, survival, and the occurrence of one or more opportunistic complications. Proportional hazards models were performed for the occurrence of death, for any opportunistic complication, and for each opportunistic complication subsequent to the 4-month visit. The time to death or the time to development of an opportunistic complication was calculated from the date of the 4-month visit and not the date of randomization. In the models for time to the occurrence of an opportunistic complication, death was considered as a censoring event if it occurred and the event under analysis did not occur in a patient. Patients with a history of certain opportunistic complications at the time of the 4-month visit were excluded from the analysis for that event because the reporting of multiple occurrences of these opportunistic conditions were not permitted in a given individual. Multiple reportings of the following conditions were not permitted: CMV disease, systemic *Mycobacterium avium* complex (MAC) infection, wasting syndrome, AIDS dementia complex (ADC), toxoplasmosis, cryptosporidiosis, cryptococcosis, progressive multifocal leukoencephalopathy, tuberculosis, other mycobacterial infections, histoplasmosis, isosporiasis, lymphoma, Kaposi's sarcoma with visceral involvement, and cervical malignancy. Multiple reportings of PCP, invasive candidiasis, invasive herpes simplex, disseminated herpes zoster, and salmonella septicemia were permitted.

In a second analysis, study participants were stratified by history of

TABLE 1. Characteristics of study participants (N = 2382)

	Mean	Standard deviation
Baseline weight (kg)	72	12.6
% Weight change at 4 months	-0.2	6.1
Absolute weight change at 4 months (kg)	-0.21	4.37
Baseline CD4 count (cells/mm ³)	85.9	84.5
Baseline Karnofsky score	88.5	9.9
Baseline hemoglobin (g/dl)	12.9	1.8
Baseline antiretroviral use (%)	67.6	
Baseline <i>Pneumocystis carinii</i> pneumonia prophylaxis (%)	89.8	
African American (%)	25.5	
Latino (%)	10.3	
Female (%)	7.1	
History of intravenous drug use (%)	19.9	
Homosexual (%)	75.7	
Age (y)	39.1	8.2
	Before study entry (%)	In first 4 months (%)
AIDS events	43.7	13.4
<i>Pneumocystis carinii</i> pneumonia	25.9	4.0
Invasive candidiasis	9.5	3.0
Wasting syndrome	6.1	1.2
Systemic <i>Mycobacterium avium</i> intercellulare complex	2.3	2.0
Cytomegalovirus disease	1.8	2.1
Other AIDS events	12.8	2.8

an opportunistic complication before study entry or during the first 4 months of observation. Proportional hazards models were again performed for the occurrence of death, and for any, or each opportunistic complication subsequent to the 4-month visit.

All models were stratified by CPCRA unit. Covariates include those listed in Table 1. One variable was used to designate a history of AIDS (Centers for Disease Control and Prevention [CDC] 1987 criteria) before study entry and one variable to designate development of an opportunistic complication during the first 4 months.

RESULTS

Between September 1990 and October 1995, 2769 participants were enrolled in four CPCRA clinical trials. From this analysis, 387 were excluded. Thirteen had CD4 counts >500 cells/mm³, 93 died before the 4-month visit, 214 were missing data for the 4-month weight, 48 answered unknown to whether they had sexual contact with someone of the same gender or whether they had used intravenous drugs, and 19 were excluded for other reasons. The mean follow-up for these individuals was 1.95 years (range, 0.04–4.85 years). Summary statistics of the baseline characteristics are given in Table 1. Twenty-six percent of the participants were African American, 10% were Latino, 20% were injection drug users, and 7% were women. The mean CD4 cell count was 86 cells/mm³ (range, 0–500 cells/mm³), and the

mean weight was 72 kg. The cohort lost an average of 0.23 kg, or 0.2% of baseline body weight, in the first 4-month period. Before study entry, 44% of participants had had an AIDS-defining illness, whereas 13% developed AIDS during the initial 4-month period of observation.

During the follow-up period, 46% of the cohort died and 51% had at least one opportunistic identified complication. Proportional hazards analyses adjusting for the covariates in Table 1 demonstrate a statistically significant increased risk of death (2.54; $p < .001$) and any opportunistic complication (1.87; $p < .001$) for individuals with $>10\%$ weight loss and (2.22; $p < .001$) and (1.89; $p < .001$) respectively for those who lost between 5% and 10% over a 4-month period relative to those with no weight loss during the same time period (Table 2). When those who lost between 0% and 5% of their body weight are compared with those who did not lose weight, the relative risks are 1.26 ($p < .01$) and 1.19 ($p < .01$) for death and any opportunistic complication, respectively. Kaplan-Meier survival plots, stratified according to CD4 cell count at baseline and amount of weight change are shown in Figure 1. The occurrence of the first opportunistic condition, stratified according to CD4 cell count and amount of weight loss are given in Figure 2. With the exception of invasive candidiasis, the relative risks of the occurrence of specific complications listed in Table 2, for patients with weight loss of 5% to 10%, relative to those with no weight loss, are all statistically significant. For those who lost $<5\%$ of their body weight, the relative risk for any opportunistic complication, for CMV disease, as well as other opportunistic infections and malignancies were also statistically significant. The relative risk of individual complications was also significantly higher in those who lost $>10\%$ body weight but this analysis was hampered by the small sample size in each group.

Those individuals with no prior history of an opportunistic complication still had an increased risk of death or an opportunistic complication if they lost 5% to 10% of their body weight over 4 months, when compared with those who did not lose weight (Table 3).

TABLE 2. Relative risk of clinical event for patients experiencing weight loss compared with those experiencing no weight loss

Event	Number of events	Adjusted RR		
		$>10\%$ weight loss	5%–10% weight loss	$<5\%$ weight loss
Death	1091	2.54 ^a	2.22 ^a	1.26 ^b
Any OC	1211	1.87 ^a	1.89 ^a	1.19 ^b
PCP	372	1.12	1.61 ^b	1.17
CMV disease	307	1.89 ^c	2.33 ^a	1.35 ^c
Invasive candidiasis	303	0.68	1.29	0.85
Systemic MAC	313	2.03 ^b	1.81 ^b	1.27
Wasting syndrome	143	3.41 ^a	2.41 ^a	1.23
ADC	133	2.24 ^c	2.76 ^a	1.17
Other OI ^d	279	2.11 ^b	2.29 ^a	1.33 ^c
Any OM ^e	137	3.58 ^b	1.65	1.52 ^c

^a $p \leq .001$.

^b $p \leq .01$.

^c $p \leq .05$.

^d Other OI includes toxoplasmosis, cryptosporidiosis, cryptococcosis, PML, disseminated herpes zoster, invasive herpes simplex, tuberculosis, other mycobacterial infections, histoplasmosis, and salmonella septicemia.

^e Any OM includes lymphoma, Kaposi's sarcoma (with visceral involvement), and cervical malignancy.

ADC, AIDS dementia complex; CMV, cytomegalovirus; MAC, *Mycobacterium avium* complex; OC, opportunistic complications; OI, opportunistic infection; OM, opportunistic malignancy; PCP, *Pneumocystis carinii* pneumonia; PML, progressive multifocal leukoencephalopathy.

DISCUSSION

We have shown that mild ($<5\%$) or moderate weight loss (between 5%–10% of body weight over a 4-month period) in an HIV-infected adult is predictive of decreased survival and an increased risk of developing an opportunistic complication. Furthermore, weight loss of as little as 5% to 10% is strongly associated with the

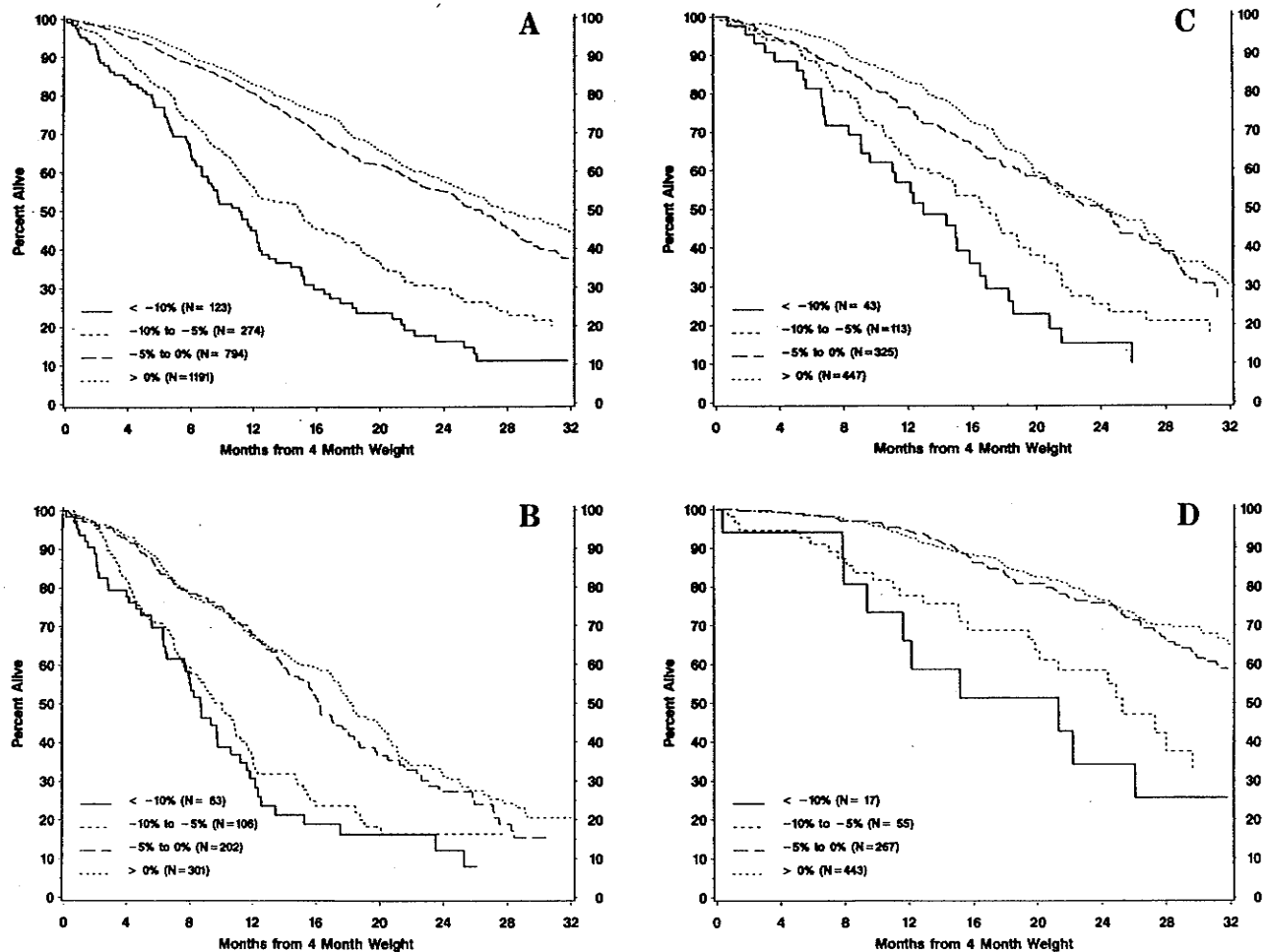


FIG. 1. Time to death by percent weight change in the first 4 months for (A) all participants, (B) those with baseline CD4 count of <25 cells/mm³, (C) those with baseline CD4 cell count of 25 to 99 cells/mm³, and (D) those with baseline CD4 cell count of 100 to 499 cells/mm³.

onset of individual opportunistic complications, including PCP, CMV disease, systemic MAC infection, and ADC. We have also shown that weight loss is predictive of decreased survival and an increased risk of future opportunistic complications, even in the absence of prior or concurrent AIDS-defining complications.

An association between severe weight loss and survival has been previously described. Kotler et al. (9) demonstrated a linear relation between the severity of tissue depletion and survival in patients with end-stage HIV infection. The study suggested that a loss of 34% of ideal body weight usually resulted in death. They also noted a similar association between weight loss and death in other conditions, such as starvation (15). In a study of HIV-infected patients who required hospitalization, Chlebowski et al. found a correlation between severe weight loss before admission and subsequent mortality (16). Patients with an admission weight of $\leq 10\%$

below their usual body weight survived 520 days, whereas patients whose weight was $>20\%$ below their usual body weight survived only 48 days. Guenter et al. (17) found a correlation between baseline body weight and survival. The risk of death for those whose weight was $<90\%$ of their usual body weight was 8.3 times higher than those who weighed $>90\%$ of their usual body weight.

In a retrospective study of gay men enrolled in the Multicenter AIDS Cohort Study (MACS), Palenicek et al. (10) demonstrated a relation between weight loss and survival. Those with weight loss of >4.5 kg over a 3- to 9-month period had a significantly shorter survival (1.06 years) than those with either <4.5 kg weight loss or those with weight gain (1.45 years). They also found that changes in weight, from baseline until 3 months before an AIDS diagnosis, correlated with survival after the AIDS diagnosis. Those with $>10\%$ loss of baseline weight, 5% to 10% loss, and $<5\%$ loss survived 0.83,

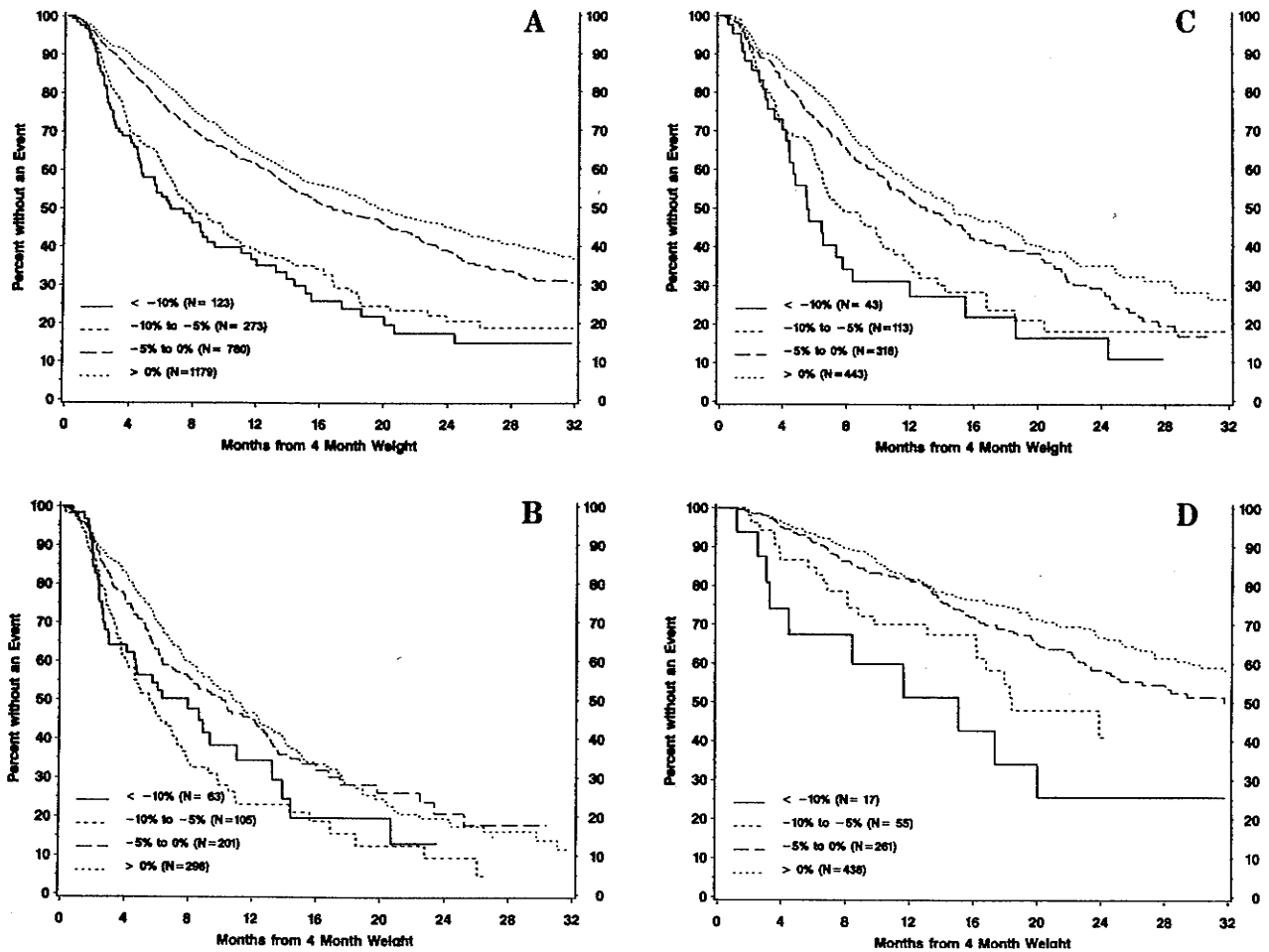


FIG. 2. Time to any opportunistic complication by percent weight change in first 4 months for (A) all participants, (B) those with baseline CD4 cell count of <25 cells/mm³, (C) those with baseline CD4 cell count of 25 to 99 cells/mm³, and (D) those with baseline CD4 cell count of 100 to 499 cells/mm³.

1.14, and 1.44 years, respectively. When controlled for other covariates, however, the survival differences were only significant between those with a >10% weight loss and those who had lost <5% of body weight.

TABLE 3. Relative risk of death or opportunistic complication for patients with weight loss compared with those with no weight loss, stratified by prior history of an opportunistic complication

Degree of weight loss	Death			Any OC		
	All	History of OC	No history of OC	All	History of OC	No history of OC
>10%	2.54 ^a	2.58 ^a	2.50 ^a	1.87 ^a	1.70 ^a	2.32 ^b
5%–10%	2.22 ^a	2.09 ^a	2.66 ^a	1.89 ^a	1.90 ^a	1.86 ^a
<5%	1.26 ^b	1.44 ^a	1.06	1.19 ^b	1.22 ^c	1.19

^a *p* < .001.

^b *p* < .01.

^c *p* < .05.

OC, opportunistic complication.

Although the relation between weight loss in HIV infection and survival has been demonstrated, our data are the first to suggest that losses of <10% and even <5% can be predictive of survival. The relative risk of dying during follow-up was 1.26 for those who lost between 0% and 5% of their body weight relative to those who did not lose weight over a 4-month period. The relative risk was 2.22 for those who lost 5% to 10% and rose to 2.54 for those who lost >10%, even when controlled for other covariates known to be associated with decreased survival.

Our analysis is also the first to demonstrate a clear relation between weight loss and an increased risk of individual opportunistic complications of HIV. Graham et al. (18) demonstrated an association between decreased body mass index in kilograms per square meters of body area and the onset of fever, AIDS diagnosis, and CD4 count of <100 cells/mm³ in the MACS; however,

no correlation with individual opportunistic infections was found. We have shown that a loss of between 0% and 5% of body weight over a 4-month period is predictive of the development of an opportunistic complication of HIV and is also predictive of the development of CMV disease. A loss of 5% to 10% is predictive of the onset of PCP, systemic MAC infection, and ADC, independent of CD4 count, use of antiretroviral chemotherapy, or the use of PCP prophylaxis.

Opportunistic infections and malignancies are frequently implicated as the underlying cause of weight loss and decreased survival (7). Our data demonstrate that weight loss of as little as 5% to 10% of body weight over 4 months is predictive of death and an increased risk of opportunistic complications, even in those with no history of a previous or concurrent opportunistic complication. This observation supports the hypothesis that a poor prognosis associated with weight loss in HIV may be partly attributed to the weight loss itself and not only to underlying opportunistic complications. Because this was a retrospective analysis, and because the presence of occult opportunistic infections cannot be excluded, further investigation is needed in order to clarify a true cause and effect relation.

Our analysis included individuals who were enrolled in CPCRA studies before availability of HIV-RNA measurements and before use of protease inhibitors in antiretroviral treatment regimens. The impact of protease inhibitor therapy on body weight is currently being evaluated. Future studies of the clinical outcomes of weight change in HIV infection will need to incorporate measurements of HIV-RNA and be designed to evaluate the effect of highly active antiretroviral therapy.

As understanding of the relation between changes in body weight and progression of HIV disease has become better defined, body weight measurements have become recognized as an important tool for monitoring clinical disease progression (19). Our data strengthen the association between weight loss and survival and demonstrate a relation between weight loss and the risk of individual opportunistic complications of HIV. Whether preservation of weight or reversal of weight loss provides any clinical benefit still needs to be investigated. It is likely that the serial collection of accurate weight measurements will become a routine component of care for HIV patients and an important outcome measure in future clinical trials of HIV-related therapy.

Acknowledgments: Supported by the National Institute of Allergy and Infectious Diseases and the Terry Bein Community Programs for Clinical Research on AIDS, Bethesda, MD, U.S.A.

REFERENCES

- Weiss PJ, Wallace MR, Olson PE, Rosetti R. Changes in the mix of AIDS defining conditions. *N Engl J Med* 1993;329:1962.
- Hoover DR, Saah AJ, Bacellar H, et al. Clinical manifestations of AIDS in the era of *Pneumocystis* prophylaxis. *N Engl J Med* 1993;329:1922-6.
- Nahlen BL, Chu SY, Nwanyanwu OC, Berkelman RL, Martinez SA, Rullan JV. HIV wasting syndrome in the United States. *AIDS* 1993;7:183-8.
- Volberding P, Kaslow K, Bilk M. Prognostic factors in staging Kaposi's sarcoma in AIDS. *Proc Am Soc Clin Oncol* 1984;3:51.
- Dworkin B, Wormser GP, Rosenthal WS. Gastrointestinal manifestations of the acquired immunodeficiency syndrome: a review of 22 cases. *Am J Gastroenterol* 1985;80:774-8.
- McCorkindale C, Dybevik K, Coulston AM, Sucher KP. Nutritional status of HIV-infected patients during the early disease stages. *J Am Diet Assoc* 1990;90:1236-41.
- Macallan DC, Noble C, Baldwin C, Foskett M, McManus T, Griffin GE. Prospective analysis of patterns of weight change in stage IV human immunodeficiency virus infection. *Am J Clin Nutr* 1993;58:417-24.
- Kotler DP, Tierney AR, Culpepper-Morgan JA, Wang J, Pierson RN. Effect of home total parenteral nutrition on body composition in patients with acquired immunodeficiency syndrome. *JPEN J Parenter Enteral Nutr* 1990;14:454-8.
- Kotler DP, Tierney AR, Wang J, Pierson RN. Magnitude of body cell mass depletion and the timing of death from wasting in AIDS. *Am J Clin Nutr* 1989;50:444-7.
- Palenicek JP, Graham NMH, He YD, et al. Weight loss prior to clinical AIDS as a predictor of survival. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995;10:366-73.
- Jacobson MA, Besch CL, Child C, et al. Primary prophylaxis with pyrimethamine for toxoplasmic encephalitis in patients with advanced HIV disease: results of a randomized trial. *J Infect Dis* 1994;169:384-94.
- Abrams DI, Goldman AI, Launer C, et al. A comparative trial of didanosine or zalcitabine after treatment with zidovudine in patients with human immunodeficiency virus infection. *N Engl J Med* 1994;330:657-2.
- Saravolatz LD, Winslow DL, Collins G, et al. Zidovudine alone or in combination with didanosine or zalcitabine in HIV infected patients with the acquired immunodeficiency syndrome or fewer than 200 CD4 cells per cubic millimeter. *N Engl J Med* 1996;335:1099-1106.
- Brosgart C, Craig C, Hillman D, et al. Final results from a randomized, placebo-controlled trial of the safety and efficacy of oral ganciclovir for prophylaxis of CMV retinal and gastrointestinal mucosal disease [abstract Th.B.301]. Presented at the XI International Conference on AIDS, Vancouver, British Columbia, Canada, July, 1996.
- Brozek J, Wells S, Keys A. Medical aspects of semistarvation in Leningrad (siege 1941-1942). *Am Rev Soviet Med* 1946;4:70-86.
- Chlebowski RT, Grosvenor MB, Bernhard NH, Morales LS, Bulcanage LM. Nutritional status, gastrointestinal dysfunction, and survival in patients with AIDS. *Am J Gastroenterol* 1989;84:1288-93.
- Guenther P, Muurahainen N, Simons G, et al. Relationship among nutritional status, disease progression, and survival. *J Acquir Immune Defic Syndr Hum Retrovirol* 1993;6:1130-8.
- Graham NMH, Munoz A, Bacellar H, Kingsley LA, Visscher BR, Phair JP. Clinical factors associated with weight loss related to infection with human immunodeficiency virus type 1 in the multicenter AIDS cohort study. *Am J Epidemiol* 1993;137:439-46.
- Grunfeld C, Feingold KR. Body weight as essential data in the management of patients with human immunodeficiency virus infection and the acquired immunodeficiency syndrome. *Am J Nutr* 1993;58:317-8.