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Long-term Impact of HIV Wasting on Physical Function in the Multicenter AIDS Cohort Study

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Abstract

Background—The long-term consequences of wasting among HIV-infected persons are not known.

Design—HIV-infected participants surviving 2 years based on Kaplan Meier analysis after a clinical diagnosis or weight trajectory consistent with wasting and with available physical function assessment data (grip strength, gait speed, and quality of life [QoL]) were matched to HIV-infected and -uninfected men without wasting.

Methods—Matching criteria at the functional assessment included age, calendar year, and CD4 cell count and plasma HIV-1 RNA (HIV-infected only). Multivariable linear regression analyses adjusted for age, cohort, race, hepatitis C status, and number of comorbid illnesses were used to assess the impact of wasting on subsequent physical function.

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Results—Among 85 HIV-infected men surviving 2 years after wasting, we evaluated physical function outcomes compared to 249 HIV-infected and 338 HIV-uninfected men with no historical wasting. In multivariable regression models, HIV-infected men with prior wasting had lower grip strength and poorer physical QoL than HIV-infected men with no wasting ($p = 0.03$), and poorer physical QoL but higher mental QoL than HIV-uninfected men ($p = 0.05$). When controlling for measures of immune suppression (nadir CD4/AIDS), the association between wasting and physical QoL was markedly attenuated, whereas there was minimal impact on the association between wasting and grip strength.

Conclusions—HIV-infected wasting survivors had weaker grip strength compared to HIV-infected persons without wasting; immune suppression was associated only with physical QoL. HIV-infected survivors of wasting may represent a population of adults at increased risk for physical function decline.

Keywords

HIV; aging; wasting; sarcopenia; frailty; falls

BACKGROUND

In 1987, a specific constellation of symptoms termed “HIV-associated wasting syndrome” was added to the case definition for AIDS, reflecting the severity of and frequency with which wasting symptoms were seen prior to the availability of highly active antiretroviral therapy (HAART) [1]. This syndrome required specific criteria for diagnosis ($>10\%$ involuntary weight loss, either chronic diarrhea or weakness, and fever for 1 month); however, general weight loss and wasting were and still remain some of the most common manifestations of advanced HIV disease [2]. Similar to wasting from other causes such as cancer or dementia, weight loss or wasting associated with HIV is characterized by a loss of both fat mass and lean body mass, and is often accompanied by muscle fatigue and weakness [3]. Though the mechanisms is uncertain, wasting is likely mediated in part by high systemic concentrations of inflammatory cytokines leading to increased energy expenditure and proteolysis [4]. Hypogonadism, hypoadrenalism, and growth hormone resistance may also contribute to the loss of lean body mass, particularly in persons with advanced HIV disease [5–7].

Since the widespread use of HAART, the incidence of wasting in HIV has decreased dramatically [8]. However, the initial loss of total body weight or lean body mass associated with unsuppressed HIV-1 replication [9] may not be fully restored with effective suppression after HAART initiation, despite decreases in pro-inflammatory cytokines, immune activation, and whole body proteolysis [10–12]. As a result, a high incidence of wasting has been seen in some cohorts in the United States, even during the HAART era [13]. Furthermore, delayed HAART initiation and resultant higher risks for opportunistic infections in many resource-limited settings contribute to the ongoing relevance of wasting in the current HAART era.

The long-term consequences of wasting among HIV-infected persons have not been well described. Studies indicated wasting in HIV is associated with decreased functional status,

increased susceptibility to opportunistic infections, and an increased risk of mortality [3, 14]. Survivors of other severe illnesses similarly can have long-term multi-system alterations. For example, survivors of childhood leukemia, brain tumors, and stem-cell transplantation show low physical performance and a high prevalence of metabolic disorders in adulthood [15–17]. Adult cancer survivors often have impairments in physical function [18–21], particularly those who experienced weight loss or weight gain during treatment [22]. These residual physical function impairments among survivors of cancer-related wasting are likely due to many factors, including hormonal alterations resulting from systemic treatment, long-term effects of radiation, changes in dietary habits, and changes in physical activity [21]. We hypothesized that HIV-infected men with a history of wasting will differ from HIV-infected or HIV-uninfected men with no prior wasting, with respect to physical function and quality of life, even years after the original diagnosis of wasting. If this hypothesis is correct, survivors of HIV-wasting may represent a group with increased risk of functional decline with aging.

Methods

Study Sample and Variable Assessment

The Multicenter AIDS Cohort Study (MACS) was established by the National Institutes of Health in 1984 as a prospective observational study of men who have sex with men who either had or were at risk for HIV infection [23], at four clinical sites: Baltimore, MD/ Washington, DC, Chicago, IL, Los Angeles, CA, and Pittsburgh, PA. Enrollment occurred during three time periods: 1984–1985, 1987–1991, and 2001–2003. At each semi-annual study visit, blood draws and physical exams were performed and the presence of HIV-related sequelae such as clinical manifestations of wasting was assessed. Self-reported use of antiretroviral medications was summarized at each visit to define prior and current use of HAART [24]. CD4+ T-cell count (CD4) was measured with standardized flow cytometry [25, 26]. Informed consent was obtained from each participant, and approval was provided by each local institutional review board.

Study Definitions and Design

To define our study population and test the validity of our definitions used for wasting, we first conducted a survival analysis including all MACS participants enrolled before the end of the 2003. We estimated the probability of survival by the presence or absence of wasting for all MACS participants, including HIV-infected (N=3577) and HIV-uninfected (N=4029, with 634 seroconverters' follow-up time before seroconversion) men. Wasting among the HIV-infected men was defined by the presence of any of the following: 1) a clinical diagnosis of HIV-wasting by medical record review, 2) a body mass index (BMI) at entry into the MACS of $<18.5 \text{ kg/m}^2$, 3) a 10% decrease from the average of the three heaviest prior weights, sustained for 2 study visits, or 4) a slope of -1 kg/year across all prior weight data. All weight trajectories from individuals with suspected wasting were visually inspected for consistency with a clinical pattern of wasting-related weight loss.

As shown in Figure 1, the median survival was markedly lower among HIV-infected men with wasting (9.1 years; 95% CI: 8.4, 9.6 years) compared to HIV-infected men with no

history of wasting (11.6 years; 95% CI 11.0, 12.4 years). The most pronounced impact on survival was seen among HIV-infected men with a negative weight slope (5.3 years; 95% CI 4.7, 6.2 years).

To determine the long-term impact of wasting among survivors for the analyses presented here, HIV-infected men that both 1) met wasting criteria (as described above) and, 2) had available assessments of grip strength and gait speed (functional outcome measures) at least 2 years following the wasting criteria attainment were selected as cases. To limit the effects of intentional weight loss, only participants with a BMI ≥ 25 kg/m² at the time of the functional outcome measures were included (N= 25 excluded). For this analysis, the visit at which wasting was first diagnosed was defined as the baseline visit, and the men were followed until the first visit with available functional outcome measures of interest, at least two years following the wasting visit.

Participants with HIV-wasting (HIV/wasting) were matched to up to four HIV-infected men without wasting (HIV/no wasting) and HIV-uninfected men at the time of the functional outcome measures, and were matched on calendar time (± 1 year), age (± 5 years), and, for HIV-infected participants, CD4 (± 100 cells/ μ L) and plasma HIV-1 RNA < 400 copies/mL (VL). In addition, cases and controls were also matched on baseline visit (± 1 year), i.e., controls were seen in a MACS study visit within a year of a case meeting a wasting diagnosis. Weight trajectories of potential wasting cases were independently reviewed for agreement in meeting wasting criteria. Outliers were reviewed by two clinicians (KME and TTB); one individual with multiple outlying weight measures was excluded.

Outcome Variables—Functional outcome measures included grip strength and time to walk 4 meters, which were measured at each semi-annual MACS visit starting in October 1, 2005. Grip strength (kg) was measured three times in the dominant hand using a Jamar Dynamometer (Patterson Medical, Warrenville, IL); the average of the three measures was used for analysis. Time (seconds) to walk 4-meters at usual pace was measured twice; the faster walk out of two attempts was used to calculate gait speed (meters/second). As a secondary outcome, we examined measures from the health-related quality of life (QoL) Medical Outcomes Study Short Form-36 Health Survey (SF-36), a self-administered, widely used and validated questionnaire [24], at each semi-annual visit. The QoL data from the SF-36 can be summarized using a composite measure of physical and mental health. The physical health component score (PCS) summarizes 4 scales critical to physical QoL: Physical Functioning, Role-Physical, Bodily Pain, and General Health. The mental health component score (MCS) summarizes 4 scales critical to mental QoL: Vitality, Role-Emotional, Social Functioning, and Mental Health. Scores are normalized to a population mean of 50 with a standard deviation of 10 [26].

Other Covariates—Other parameters were assessed that could affect the relationship between wasting and a loss of physical functioning. Cohort effects were dichotomized into participants enrolled prior to 2001, or during 2001–2003. Race was dichotomized as white or non-white, cigarette smoking as ever or never, and heavy alcohol use as self-report of regular consumption of >14 drinks/week (versus less) at one or more visits from the baseline

to the functional outcome measures assessment. Hepatitis C virus (HCV) infection at the functional outcomes measures assessment was defined as a detectable hepatitis C virus (HCV) RNA level in serum; men who lacked HCV RNA were considered uninfected with HCV. The comorbidity score was defined as the total number of the following comorbid conditions present at the time of the functional outcome measures assessment: 1) depression (Centers for Epidemiologic Studies Depression Scale score > 16 [27]), 2) hypertension (systolic blood pressure >140 mmHg or diastolic pressure >90 mmHg), 3) diabetes mellitus (fasting glucose ≥126 mg/dL, or self-report of a clinical diagnosis with use of anti-diabetic medication), 4) dyslipidemia (either fasting total cholesterol ≥200 mg/dL, low-density lipoprotein ≥130 mg/dL, high-density lipoprotein <40 mg/dL, triglycerides ≥150 mg/dL, or use of lipid-lowering medications with self-report of a clinical diagnosis), 5) kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m² using the Modification of Diet in Renal Disease equation [28] or a urine protein-to-creatinine ratio ≥200 mg protein/1 g creatinine), 6) liver disease (alanine transaminase or aspartate aminotransferase >150 IU/L), 7) cancer within 1 year (diagnosis at or within a year of the functional outcome measures assessment visit [29]). HIV-related variables at the time of the functional outcome measures included the time since HIV diagnosis (in years), current and cumulative use of any HAART, current and cumulative use of zidovudine (ZDV) or stavudine (D4T), current and cumulative use of protease inhibitor (PI) therapy, current CD4 (per 100 cells/μL), nadir CD4 cell count (<200 vs. ≥200 cells/μL), history of clinical AIDS diagnosis, and the time with virologic control (percentage of visits with plasma HIV-1 RNA <400 copies/mL between the baseline to the functional outcome measures).

Statistical Analysis

Grip strength, gait speed, and the mental and physical health summary scores from the SF-36 were each regressed on wasting group (HIV/wasting [reference group], HIV/no wasting, HIV-uninfected) using multivariable linear regression to assess the impact of wasting exposure on later physical functioning and quality of life. Each model included age, race, HCV status, number of comorbidities, and cohort (before 2001, or 2001–2003 MACS enrollment). Smoking, heavy alcohol use, and time from the baseline visit were not associated with any physical function or QoL outcomes ($p>0.10$) and were not included in the final models. Among HIV-infected participants only, we examined each HIV variable in separate models, adjusting for age, race, HCV status, number of comorbidities, and cohort. HIV-specific variables with a p value of <0.10 in these models were included in the multivariable regression models for HIV-infected participants. Of the HIV-specific variables (time since HIV diagnosis; current/cumulative use of any HAART, ZDV, D4T, or PI; current or nadir CD4, history of clinical AIDS diagnosis, and the time with virologic control), only virologic control, nadir CD4, and history of clinical AIDS had a $p<0.10$ for any of the four outcomes and were introduced in the respective models.

Results

Of the 85 HIV-infected men who survived for at least two years after a wasting diagnosis (HIV/wasting) and had available, complete functional outcome measures, 16 men had a clinical diagnosis of HIV-wasting, 3 had both a clinical wasting diagnosis and weight loss

criteria, and 66 met at least one weight loss criteria (low BMI, sustained weight loss or negative trajectory). These HIV/wasting men were matched to 249 HIV/no wasting and 338 HIV-uninfected men. Although the wasting visits ranged from 1984 to 2012, 80% of visits occurred after 1996. At the time of the wasting visit, HIV/wasting men were similar in age to HIV/no wasting and HIV-uninfected men (Table 1). HIV/wasting men tended to have a lower current and nadir CD4 count, a longer duration of HAART, and a greater frequency of current or prior ZDV or D4T treatment compared to HIV-infected men without wasting. At the time of the functional assessment, HIV/wasting men had more comorbidities (median: 2 vs 1 comorbidities), a lower proportion of visits with suppressed HIV RNA (82 vs 91%), a greater proportion of prior D4T use (69 vs 54%), and greater use of therapies directed against wasting (testosterone, anabolic steroids, growth hormone, or megestrol). Other characteristics were similar and are detailed in Table 1.

Between the wasting visit and the functional outcome measures assessment (median 4.1 years), the HIV/wasting men had a small but significant increase in total body weight, while the HIV/no wasting and HIV-uninfected men remained relatively stable, respectively (Figure 2). As shown in Table 1, despite an increase in weight between visits, the HIV/wasting men weighed less than HIV/no wasting and HIV-uninfected men, with a nearly 10 kg difference at the wasting visit and a persistent 8 to 9 kg difference at the functional outcome measures visit.

In multiple linear regression models including both HIV-infected and uninfected participants (adjusted for age, cohort, race, hepatitis C virus infection, and number of comorbidities), a history of HIV-wasting was associated with both lower grip strength and poorer physical QoL compared to HIV/no wasting, and with poorer physical QoL compared to HIV-uninfected men (Figure 3, Table 2). Mental QoL was better among HIV/wasting compared to HIV-uninfected men ($p=0.05$), but was not significantly different from HIV/no wasting men. Gait speed was not significantly different between HIV/wasting, and HIV/no wasting or HIV-uninfected men ($p=0.13$).

In regression models restricted to HIV-infected participants (Table 2), the association between wasting and physical QoL was markedly attenuated and no longer significant when the nadir CD4 and clinical AIDS were added to the model. No HIV variables were significant predictors of low grip strength, gait speed, or mental QoL. Increased age was the only significant predictor of all outcomes: lower grip strength, slower gait speed, poor physical QoL, and higher mental QoL. Mental QoL was negatively associated with greater comorbid disease burden and positively associated with older age (all $p<0.001$). In models limited to the HIV-infected participants, the effect of wasting on grip strength was slightly attenuated (2.4 kg to 2.3 kg) and was no longer statistically significant ($p=0.055$). To further investigate the potential impact of immunosuppression on grip strength, an additional model was created where nadir CD4 and history of clinical AIDS were forced into the final regression. The effect of wasting on grip strength was minimally changed compared to the findings in Table 2 (estimate 2.3 kg, 95% CI $-0.2, 4.7$; $p=0.073$) and nadir CD4 and history of clinical AIDS were not associated with grip strength ($p=0.90$).

Discussion

Here we report upon the long-term consequences of HIV-wasting among men who survived the initial illness and who, for the most part, received virally suppressive HAART. First, in establishing the weight loss definitions for our cohort, similar to findings from prior studies, we found that the occurrence of HIV-wasting by any of our tested definitions was associated with markedly shorter survival than observed among HIV-infected men without wasting or uninfected men (Figure 1) [2, 27]. A strong association between mortality and weight loss, independent of underlying disease or comorbid illnesses, has been well-described among older, HIV-uninfected adults [28–32]. One longitudinal study found increased mortality among older adults (mean age 73) who experienced any appreciable weight loss after the age of 21 [29]. Reports among HIV-infected participants are more limited but similar in implication: in the Nutrition for Healthy Living cohort, weight loss from baseline weight and weight loss of 5% or more over a 6-month period were significant predictors of mortality [13, 27]. Furthermore, among older adults, having an underweight body type between the 3rd and 8th decade of life has been associated with poorer survival [29].

Men with wasting in our cohort did gain small but significant amounts of body weight during the time between wasting diagnosis and subsequent functional outcome measures visits, but body weight remained an average of nearly 10 kg less than that observed among the men without a history of wasting. Among older men with 3% weight loss in the Health Aging and Body Composition Study, 60% of weight loss represented loss of lean mass, a surrogate for skeletal muscle mass, and only 21% of weight regained was lean mass [33]. Although we did not have available measures of body composition, we suspect that wasting in our cohort was associated largely with losses in lean mass, with subsequent weight regain largely representing fat mass. Little is known about the impact of weight changes on mortality by HIV serostatus among older adults. In a recent study, weight gain among underweight and normal-weight HIV-infected individuals receiving HAART improved survival, using a minimum threshold of a 4.5–9.0 kg weight gain within the first year after HAART initiation [34]. The persistent low body weight and mean gain of only 2 kg over 4 years is of particular concern in regards to long-term consequences in our cohort.

Of the functional measures, the greater impact of wasting on grip strength and physical QoL rather than gait speed (Table 2) may be the consequence of the losses in lean body mass associated with HIV-wasting and subsequent failure to regain lean body mass. The degree of impairment observed among HIV/wasting men may have significant clinical implications. For comparison, a loss of approximately 4 kg of grip strength is seen for each decade of advancing age among men aged 50 and older, suggesting that the 2 kg effect of wasting is similar to the effect of 5 additional years of aging [35]. Similarly, the decline of 2 to 5 points on physical QoL scores that was associated with HIV-wasting is similar to the 2 to 3 point decline seen with each decade of advancing age in a normative population, suggesting that HIV-wasting had a similar effect as 10 to 20 years of aging on self-reported physical QoL [36].

Despite physical limitations in strength and the perception of poorer physical QoL, the HIV/wasting men had significantly higher mental QoL compared to HIV/no wasting men. In

many other disease processes, wasting and/or low BMI are associated with poor QoL and decreased response to QoL interventions, so this was an unexpected finding [37–39]. Prior studies involving older HIV-infected adults have found a strong association between greater resilience and improved mental QoL [40]. Perhaps the greater mental QoL is due in part to a greater appreciation of survival following advanced disease, or to a realization of partial disease “remission” with continued HIV [41, 42],

In the models restricted to HIV-infected men, grip strength was the only outcome that was associated with HIV-wasting, albeit this no longer reached statistical significance, likely a reflection of the sample size as the effect size was minimally changed. In contrast, the association between wasting and physical QoL was markedly attenuated with inclusion of HIV measures. Of note, physical QoL was the only outcome significantly influenced by any HIV measures, here by measures of historical immune suppression (nadir CD4 and clinical AIDS diagnosis).

This study had several limitations. The number of individuals surviving a history of wasting with available functional measures was small, thus we were limited in our power to detect associations in our multivariable models. We cannot rule out intentional weight loss among persons with wasting, though we attempted to limit this possibility by only including participants with BMI less than 25 kg/m². The cause of wasting among HIV-infected persons is often multifactorial. Although we attempted to account for underlying diseases, we were unable to assess the impact of food insecurity, amount or types of dietary intake, malabsorption, or other factors such as poor dentition that may impact food intake.

In conclusion, HIV-wasting has a negative impact on muscle strength and physical QoL, years after stabilization of body weight. Although the association between wasting and physical QoL is largely attributed to prior immune suppression, HIV measures had minimal impact on the association between wasting and grip strength. Prior studies have demonstrated that low body weight and/or poor strength are associated with low bone density [43–45], injurious falls [46–48], fractures [45, 49], frailty [50–52] and, ultimately, could result in a loss of independent living. Furthermore, unintended weight loss or a negative weight trajectory portends a poor survival among HIV-infected persons and, as shown in prior studies, is a stronger predictor of risk for death than decreases in other measures of fat mass, lean mass, or body cell mass [13, 27]. With the burgeoning obesity epidemic, routine screening and identification of overweight or obese individuals have been implemented in many clinical settings. Similar efforts to improve identification of individuals with a negative weight trajectory could have important clinical implications, providing the clinician and patient an opportunity to diagnose and treat the underlying factors contributing to weight loss and attenuate the long-term consequences of HIV-wasting.

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References

1. Stehr-Green JK, Jason JM, Evatt BL. Potential effect of revising the CDC surveillance case definition for AIDS. *Lancet*. 1988; 1:520–521. [PubMed: 2893928]
2. Wanke CA, Silva M, Knox TA, Forrester J, Speigelman D, Gorbach SL. Weight loss and wasting remain common complications in individuals infected with human immunodeficiency virus in the era of highly active antiretroviral therapy. *Clin Infect Dis*. 2000; 31:803–805. [PubMed: 11017833]
3. Grinspoon S, Mulligan K, Department of H, Human Services Working Group on the P, Treatment of W. Weight L. Weight loss and wasting in patients infected with human immunodeficiency virus. *Clin Infect Dis*. 2003; 36:S69–78. [PubMed: 12652374]
4. Melchior JC, Salmon D, Rigaud D, Leport C, Bouvet E, Detruichis P, et al. Resting energy expenditure is increased in stable, malnourished HIV-infected patients. *Am J Clin Nutr*. 1991; 53:437–441. [PubMed: 1989410]
5. Grinspoon S, Corcoran C, Lee K, Burrows B, Hubbard J, Katznelson L, et al. Loss of lean body and muscle mass correlates with androgen levels in hypogonadal men with acquired immunodeficiency syndrome and wasting. *J Clin Endocrinol Metab*. 1996; 81:4051–4058. [PubMed: 8923860]
6. Dobs AS, Few WL 3rd, Blackman MR, Harman SM, Hoover DR, Graham NM. Serum hormones in men with human immunodeficiency virus-associated wasting. *J Clin Endocrinol Metab*. 1996; 81:4108–4112. [PubMed: 8923868]
7. Christeff N, Melchior JC, Mammes O, Gherbi N, Dalle MT, Nunez EA. Correlation between increased cortisol:DHEA ratio and malnutrition in HIV-positive men. *Nutrition*. 1999; 15:534–539. [PubMed: 10422082]
8. Smit E, Skolasky RL, Dobs AS, Calhoun BC, Visscher BR, Palella FJ, et al. Changes in the incidence and predictors of wasting syndrome related to human immunodeficiency virus infection, 1987–1999. *Am J Epidemiol*. 2002; 156:211–218. [PubMed: 12142255]
9. Shikuma CM, Zackin R, Sattler F, Mildvan D, Nyangweso P, Alston B, et al. Changes in weight and lean body mass during highly active antiretroviral therapy. *Clin Infect Dis*. 2004; 39:1223–1230. [PubMed: 15486848]
10. Aukrust P, Haug CJ, Ueland T, Lien E, Muller F, Espevik T, et al. Decreased bone formative and enhanced resorptive markers in human immunodeficiency virus infection: indication of normalization of the bone-remodeling process during highly active antiretroviral therapy. *J Clin Endocrinol Metab*. 1999; 84:145–150. [PubMed: 9920075]
11. Wada NI, Jacobson LP, Margolick JB, Breen EC, Macatangay B, Penugonda S, et al. The effect of HAART-induced HIV suppression on circulating markers of inflammation and immune activation. *AIDS*. 2015; 29:463–471. [PubMed: 25630041]
12. Yarasheski KE, Smith SR, Powderly WG. Reducing plasma HIV RNA improves muscle amino acid metabolism. *Am J Physiol Endocrinol Metab*. 2005; 288:E278–284. [PubMed: 15367396]
13. Mangili A, Murman DH, Zampini AM, Wanke CA. Nutrition and HIV infection: review of weight loss and wasting in the era of highly active antiretroviral therapy from the nutrition for healthy living cohort. *Clin Infect Dis*. 2006; 42:836–842. [PubMed: 16477562]
14. Kotler DP, Tierney AR, Wang J, Pierson RN Jr. Magnitude of body-cell-mass depletion and the timing of death from wasting in AIDS. *Am J Clin Nutr*. 1989; 50:444–447. [PubMed: 2773823]

15. van Waas M, Neggers SJ, van der Lelij AJ, Pieters R, van den Heuvel-Eibrink MM. The metabolic syndrome in adult survivors of childhood cancer, a review. *J Pediatr Hematol Oncol.* 2010; 32:171–179. [PubMed: 20186100]
16. Hartman A, van den Bos C, Stijnen T, Pieters R. Decrease in peripheral muscle strength and ankle dorsiflexion as long-term side effects of treatment for childhood cancer. *Pediatr Blood Cancer.* 2008; 50:833–837. [PubMed: 17763466]
17. Nuver J, Smit AJ, Wolffenbuttel BH, Sluiter WJ, Hoekstra HJ, Sleijfer DT, et al. The metabolic syndrome and disturbances in hormone levels in long-term survivors of disseminated testicular cancer. *J Clin Oncol.* 2005; 23:3718–3725. [PubMed: 15738540]
18. Ihira H, Mizumoto A, Makino K, Yasuda K, Yoko Y, Saitoh S, et al. Physical functions, health-related outcomes, nutritional status, and blood markers in community-dwelling cancer survivors aged 75 years and older. *Asian Pac J Cancer Prev.* 2014; 15:3305–3310. [PubMed: 24815487]
19. Campbell KL, Pusic AL, Zucker DS, McNeely ML, Binkley JM, Cheville AL, et al. A prospective model of care for breast cancer rehabilitation: function. *Cancer.* 2012; 118:2300–2311. [PubMed: 22488704]
20. Alibhai SM, Breunis H, Timilshina N, Johnston C, Tomlinson G, Tannock I, et al. Impact of androgen-deprivation therapy on physical function and quality of life in men with nonmetastatic prostate cancer. *J Clin Oncol.* 2010; 28:5038–5045. [PubMed: 21041715]
21. Christensen JF, Jones LW, Andersen JL, Dagaard G, Rorth M, Hojman P. Muscle dysfunction in cancer patients. *Ann Oncol.* 2014; 25:947–958. [PubMed: 24401927]
22. Young A, Weltzien E, Kwan M, Castillo A, Caan B, Kroenke CH. Pre- to post-diagnosis weight change and associations with physical functional limitations in breast cancer survivors. *J Cancer Surviv.* 2014; 8:539–547. [PubMed: 24806261]
23. Kaslow RA, Ostrow DG, Detels R, Phair JP, Polk BF, Rinaldo CR Jr. The Multicenter AIDS Cohort Study: rationale, organization, and selected characteristics of the participants. *Am J Epidemiol.* 1987; 126:310–318. [PubMed: 3300281]
24. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Department of Health and Human Services. Available at: <http://aidsinfo.nih.gov/guidelines>. Section accessed: 12/15/2014
25. Schenker EL, Hultin LE, Bauer KD, Ferbas J, Margolick JB, Giorgi JV. Evaluation of a dual-color flow cytometry immunophenotyping panel in a multicenter quality assurance program. *Cytometry.* 1993; 14:307–317. [PubMed: 8472607]
26. Hultin LE, Menendez FA, Hultin PM, Jamieson BD, O’Gorman MR, Borowski L, et al. Assessing immunophenotyping performance: proficiency-validation for adopting improved flow cytometry methods. *Cytometry B Clin Cytom.* 2007; 72:249–255. [PubMed: 17205569]
27. Tang AM, Forrester J, Spiegelman D, Knox TA, Tchetgen E, Gorbach SL. Weight loss and survival in HIV-positive patients in the era of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2002; 31:230–236. [PubMed: 12394802]
28. Dahl AK, Fauth EB, Ernsth-Bravell M, Hassing LB, Ram N, Gerstoft D. Body mass index, change in body mass index, and survival in old and very old persons. *J Am Geriatr Soc.* 2013; 61:512–518. [PubMed: 23452127]
29. Corrada MM, Kawas CH, Mozaffar F, Paganini-Hill A. Association of body mass index and weight change with all-cause mortality in the elderly. *Am J Epidemiol.* 2006; 163:938–949. [PubMed: 16641311]
30. Lee CG, Boyko EJ, Nielson CM, Stefanick ML, Bauer DC, Hoffman AR, et al. Mortality risk in older men associated with changes in weight, lean mass, and fat mass. *J Am Geriatr Soc.* 2011; 59:233–240. [PubMed: 21288234]
31. Somes GW, Kritchevsky SB, Shorr RI, Pahor M, Applegate WB. Body mass index, weight change, and death in older adults: the systolic hypertension in the elderly program. *Am J Epidemiol.* 2002; 156:132–138. [PubMed: 12117704]
32. Harrington M, Gibson S, Cottrell RC. A review and meta-analysis of the effect of weight loss on all-cause mortality risk. *Nutr Res Rev.* 2009; 22:93–108. [PubMed: 19555520]

33. Newman AB, Lee JS, Visser M, Goodpaster BH, Kritchevsky SB, Tylavsky FA, et al. Weight change and the conservation of lean mass in old age: the Health, Aging and Body Composition Study. *Am J Clin Nutr*. 2005; 82:872–878. quiz 915–876. [PubMed: 16210719]
34. Yuh B, Tate J, Butt AA, Crothers K, Freiberg M, Leaf D, et al. Weight change after antiretroviral therapy and mortality. *Clin Infect Dis*. 2015; 60:1852–1859. [PubMed: 25761868]
35. Yorke AM, Curtis AB, Shoemaker M, Vangsnes E. Grip Strength Values Stratified by Age, Gender, and Chronic Disease Status in Adults Aged 50 Years and Older. *J Geriatr Phys Ther*. 2015; 38:115–121. [PubMed: 25594523]
36. US Population Norms. <http://www.sf-36.org/research/sf98norms.pdf>
37. Morone G, Iosa M, Fusco A, Scappaticci A, Alcuri MR, Saraceni VM, et al. Effects of a multidisciplinary educational rehabilitative intervention in breast cancer survivors: the role of body image on quality of life outcomes. *ScientificWorldJournal*. 2014; 2014:451935. [PubMed: 25405222]
38. Rizzoli R, Reginster JY, Arnal JF, Bautmans I, Beaudart C, Bischoff-Ferrari H, et al. Quality of life in sarcopenia and frailty. *Calcif Tissue Int*. 2013; 93:101–120. [PubMed: 23828275]
39. Fukuda W, Omoto A, Ohta T, Majima S, Kimura T, Tanaka T, et al. Low body mass index is associated with impaired quality of life in patients with rheumatoid arthritis. *Int J Rheum Dis*. 2013; 16:297–302. [PubMed: 23981751]
40. Fang X, Vincent W, Calabrese SK, Heckman TG, Sikkema KJ, Humphries DL, et al. Resilience, stress, and life quality in older adults living with HIV/AIDS. *Aging Ment Health*. 2015:1–7.
41. Emler CA, Tozay S, Raveis VH. “I’m not going to die from the AIDS”: resilience in aging with HIV disease. *Gerontologist*. 2011; 51:101–111. [PubMed: 20650948]
42. Poindexter C, Shippy RA. Networks of older New Yorkers with HIV: fragility, resilience, and transformation. *AIDS Patient Care STDS*. 2008; 22:723–733. [PubMed: 18754703]
43. Kooij KW, Wit FW, Bisschop PH, Schouten J, Stolte IG, Prins M, et al. Low bone mineral density in patients with well-suppressed HIV infection: association with body weight, smoking, and prior advanced HIV disease. *J Infect Dis*. 2015; 211:539–548. [PubMed: 25180239]
44. Edelstein SL, Barrett-Connor E. Relation between body size and bone mineral density in elderly men and women. *Am J Epidemiol*. 1993; 138:160–169. [PubMed: 8356959]
45. Dong HV, Cortes YI, Shiao S, Yin MT. Osteoporosis and fractures in HIV/hepatitis C virus coinfection: a systematic review and meta-analysis. *AIDS*. 2014; 28:2119–2131. [PubMed: 24977441]
46. Levine IC, Bhan S, Laing AC. The effects of body mass index and sex on impact force and effective pelvic stiffness during simulated lateral falls. *Clin Biomech (Bristol, Avon)*. 2013; 28:1026–1033.
47. Honeycutt PH, Ramsey P. Factors contributing to falls in elderly men living in the community. *Geriatr Nurs*. 2002; 23:250–255. [PubMed: 12386601]
48. Erlandson KM, Allshouse AA, Jankowski CM, Duong S, MaWhinney S, Kohrt WM, et al. Risk factors for falls in HIV-infected persons. *J Acquir Immune Defic Syndr*. 2012; 61:484–489. [PubMed: 23143526]
49. Tanaka S, Kuroda T, Saito M, Shiraki M. Overweight/obesity and underweight are both risk factors for osteoporotic fractures at different sites in Japanese postmenopausal women. *Osteoporos Int*. 2013; 24:69–76. [PubMed: 23229467]
50. Erlandson KM, Allshouse AA, Jankowski CM, Duong S, Mawhinney S, Kohrt WM, et al. Comparison of functional status instruments in HIV-infected adults on effective antiretroviral therapy. *HIV Clin Trials*. 2012; 13:324–334. [PubMed: 23195670]
51. Langlois JA, Visser M, Davidovic LS, Maggi S, Li G, Harris TB. Hip fracture risk in older white men is associated with change in body weight from age 50 years to old age. *Arch Intern Med*. 1998; 158:990–996. [PubMed: 9588432]
52. Woods NF, LaCroix AZ, Gray SL, Aragaki A, Cochrane BB, Brunner RL, et al. Frailty: emergence and consequences in women aged 65 and older in the Women’s Health Initiative Observational Study. *J Am Geriatr Soc*. 2005; 53:1321–1330. [PubMed: 16078957]

Figure 1.
Probability of survival with or without the presence of wasting among all participants of the Multicenter AIDS Cohort Study.

Figure 2. Change in body weight between wasting and function and functional outcome measures

Unadjusted means (dots) and 95% confidence limits (bars) of the change in body weight over the interval from wasting to functional outcome measures among HIV-infected men with a wasting history (left bars), HIV-infected men with no wasting history (center bars), and HIV-uninfected men (right bars).

Figure 3. Adjusted functional outcome measures

Adjusted means (dots) and 95% confidence limits (bars) of grip strength (panel A), gait speed (panel B), physical component summary score (panel C), and mental component summary score (panel D) among HIV-infected men with a history of wasting (left bars), HIV-infected men with no history of wasting (center bars), and HIV-uninfected men (right bars) from multiple linear regression models adjusting for age, race, HCV-infection, comorbidities and cohort enrollment.

Table 1

Study population characteristics, at the time of wasting visit and at time of functional outcomes assessment (or matched visit for controls without wasting)

Characteristics	HIV+, Wasting N=85	HIV+, No Wasting N=249	HIV-, No Wasting N=338
Baseline Visit			
Year of wasting visit	2002 (1997, 2007)	2003 (1998, 2008)	2003 (1996, 2007)
Wasting visit after January 1996, N (%)	68 (80)	219 (88)	265 (78)
Age (years)	46 (42, 55)	46 (41, 53)	47 (43,565)
Cohort 2001–2003, N (%) [†]	17 (20)	108 (43)	77 (23)
White, N (%)	71 (76)	175 (64)	302 (82)
BMI (kg/m ²)	20.3 (18.7, 21.4)	23.2 (21.9, 24.9)	22.8 (21.5, 24.2)
Weight (kg)	63 (59, 68)	73 (68, 79)	73 (66, 79)
CD4 cell count (cells/μL)	435 (230, 617)	508 (350, 669)	NA
Nadir CD4 cell count (cells/μL)	228 (78,380)	291 (181,432)	NA
Viral load < 400 copies/ml, N (%)	44 (59)	134 (58)	NA
HAART			NA
Ever, N (%)	56 (66)	153 (61)	NA
Cumulative (years)	3.8 (0, 6.5)	3.2 (0, 7.1)	NA
ZDV			NA
Ever, N (%)	57 (67)	145 (58)	NA
Cumulative (years)	2 (0, 5)	1.7 (0, 5.7)	NA
D4T			NA
Ever, N (%)	49 (58)	96 (39)	NA
Cumulative (years)	0.8 (0, 3.5)	0 (0, 1.9)	NA
PI			NA
Ever, N (%)	51 (60)	124 (50)	NA
Cumulative (years)	1.7 (0, 3.9)	1.1 (0, 5.4)	NA
Functional Outcome Measures Assessment			
Time between Visits (years)	4.3 (2.4, 9.7)	4.1 (2.4, 8.7)	3.9 (2, 10)
BMI (kg/m ²)	20.9 (19.4, 22.1)	23.4 (22.1, 24.2)	23.5 (21.9, 24.3)
Weight (kg)	65 (60, 70)	73 (68,78)	74 (67, 79)
Current smoking, N (%)	33 (36)	89 (33)	72 (20)
Past smoking, N (%)	40 (48)	101 (41)	192 (57)
Alcohol use >=14 drinks/week, N (%)	3 (4)	17 (7)	33 (10)
HCV-infection, N (%)	12 (14)	32 (13)	10 (3)
Comorbidity score, Median (IQR)	2 (1,2)	1 (1,2)	1 (0,2)
CD4 cell count (cells/μL)	491(347,652)	518 (366,678)	NA
% of visits [*] with viral load < 400 copies/ml, median (IQR)	82 (52,100)	91 (60,100)	NA
HAART			NA
Ever, N (%)	81 (95)	242 (97)	NA
Cumulative (years)	8.8 (6.7,10.2)	8 (4.8,10)	NA

Characteristics	HIV+, Wasting N=85	HIV+, No Wasting N=249	HIV-, No Wasting N=338
ZDV			NA
Ever, N (%)	65 (76)	187 (75)	NA
Cumulative (years)	3.2 (0.3,6.3)	3.7 (0.1,7.1)	NA
D4T			NA
Ever, N (%)	59 (69)	134 (54)	NA
Cumulative (years)	2.1 (0, 5.3)	0.5 (0, 4.0)	NA
Protease inhibitor			NA
Ever, N (%)	72 (85)	187 (75)	NA
Cumulative (years)	6.2 (1.9, 9.0)	4.5 (0.3, 7.6)	NA
Testosterone use, ever, N [%]	32 (38)	56 (22)	0 (0)
Anabolic steroid therapy, ever, N (%)	6 (7)	0 (0)	0 (0)
Growth hormone, ever, N (%)	4 (5)	0 (0)	0 (0)
Megesterol, ever, N (%)	14 (16)	0 (0)	0 (0)
Dronabinol, ever, N (%)	12 (14)	0 (0)	0 (0)

Data shown as median (IQR) or N (%)

* between wasting and grip strength visit

[†] Cohorts included those enrolled between 2001–2003 or participants enrolled prior to 2001

Table 2

Effects of wasting and covariates on physical function measures from multiple linear regression models among all participants and among HIV-infected participants only

Parameter	Grip strength (kg)		p-value	Gait speed (m/sec)		p-value	Physical QoL Score		p-value	Mental QoL Score		p-value
	Estimate (95% CI)			Estimate (95% CI)			Estimate (95% CI)			Estimate (95% CI)		
All Participants												
Intercept	37.0 (34.2, 39.8)		<0.001	1.165 (1.093,1.237)		<0.001	49.6 (46.7,52.4)		<0.001	55.6 (52.1, 59.0)		<0.001
HIV-uninfected vs. HIV/wasting	2.1 (-0.1, 4.3)		0.058	0.042 (-0.014, 0.098)		0.14	4.8 (2.5,7.0)		<0.001	-2.7 (-5.4, 0)		0.05
HIV/no wasting vs. HIV/wasting	2.4 (0.2, 4.7)		0.03	0.044 (-0.013, 0.101)		0.13	2.8 (0.5,5.1)		0.016	-0.8 (-3.6, 2.0)		0.57
Age per 1 year (centered at 54)	-0.2 (-0.3, -0.1)		<0.001	-0.006 (-0.009, -0.003)		<0.001	-0.1 (-0.2,0)		0.014	0.3 (0.2, 0.4)		<0.001
White vs. non-white	0.3 (-1.5, 2.2)		0.72	0.038 (-0.01, 0.086)		0.12	1.1 (-0.8,3.0)		0.25	0.3(-2.0, 2.5)		0.82
Hepatitis C co-infection	-0.9 (-3.5, 1.7)		0.51	-0.078 (-0.145, -0.01)		0.024	-1.9 (-4.5,0.7)		0.15	-2 (-5.2, 1.1)		0.21
Comorbidity score, per 1 comorbidity	-0.9 (-1.7, -0.2)		0.013	-0.022 (-0.041, -0.003)		0.024	-1.8 (-2.5, -1.1)		<0.001	-2.8 (-3.6, -1.9)		<0.001
Cohort 2001-03 vs. pre-2001	-1.5 (-3.3, 0.4)		0.13	-0.063 (-0.111, -0.015)		0.01	-1.7 (-3.5,0.2)		0.08	1.7 (-0.5,4.0)		0.14
HIV-Infected Participants Only												
Intercept	37.3 (33.9,40.7)		<0.001	1.2 (1.115,1.286)		<0.001	52.2 (48.8, 55.6)		<0.001	55.9 (51.8, 60.0)		<0.001
No wasting vs. wasting	2.3 (0, 4.7)		0.055	0.046 (-0.013, 0.105)		0.13	1.4 (-1.3,7)		0.26	-0.7 (-3.5, 2.0)		0.61
Age per 1 year (centered at 54)	-0.2 (-0.4, -0.1)		0.002	-0.007 (-0.01, -0.003)		<0.001	-0.3 (-0.4, -0.1)		<0.001	0.3 (0.2, 0.5)		<0.001
White vs. non-white	0.2 (-2.3,2.8)		0.86	0.026 (-0.038,0.09)		0.427	1.8 (-0.6,4.2)		0.14	-0.3 (-3.1, 2.6)		0.84
Hepatitis C co-infection	-2.2 (-5.3,0.9)		0.17	-0.09 (-0.168, -0.012)		0.024	-1.3 (-4.3,1.6)		0.37	-3.1 (-6.7, 0.4)		0.081
Comorbidity score, per 1 comorbidity	-1.0 (-2.0)		0.062	-0.033 (-0.059, -0.008)		0.01	-1.5 (-2.5, -0.5)		0.002	-2.1 (-3.2, -0.9)		<0.001
Cohort 2001-03 vs. pre-2001	-1.2 (-3.8,1.4)		0.38	-0.089 (-0.154, -0.024)		0.007	-2.5 (-5, -0.1)		0.042	1.3 (-1.7, 4.3)		0.40
Visits with HIV-1 RNA <400 copies/mL (<75% vs. 75%)*	----			----			----			-2.4 (-4.9, 0.1)		0.061
Nadir CD4 <200 vs 200 cells/ μ L*	----			----			-3.3 (-5.3, -1.3)		0.001	----		
History of clinical AIDS diagnosis*	----			----			-3.7 (-6.4, -1.0)		0.007	----		

CI, confidence interval; QoL, quality of life by the Short Form (SF)-36; comorbidity score included depression, hypertension, diabetes mellitus, dyslipidemia, kidney disease, liver disease, or cancer.

* Included in multivariate models only if $p < 0.10$ in univariate models, adjusted for age, race, hepatitis C, comorbidity, and cohort.