

Relationship Between a Frailty-Related Phenotype and Progressive Deterioration of the Immune System in HIV-Infected Men

Loic Desquilbet, PhD,* Joseph B. Margolick, MD, PhD,† Linda P. Fried, MD, MPH,‡
John P. Phair, MD,§ Beth D. Jamieson, PhD,|| Marcy Holloway, MPAS,¶ and
Lisa P. Jacobson, ScD* for the Multicenter AIDS Cohort Study

Context: Immunological similarities have been noted between HIV-infected individuals and older HIV-negative adults. Immunologic alterations with aging have been noted in frailty in older adults, a clinical syndrome of high risk for mortality and other adverse outcomes. Using a frailty-related phenotype (FRP), we investigated in the Multicenter AIDS Cohort Study whether progressive deterioration of the immune system among HIV-positive individuals independently predicts onset of FRP.

Methods: FRP was evaluated semiannually in 1046 HIV-infected men from 1994 to 2005. CD4 T-cell count and plasma viral load were evaluated as predictors of FRP by logistic regression (generalized estimating equations), adjusting for age, ethnicity, educational level, AIDS status, and treatment era [pre–highly active antiretroviral therapy (HAART) (1994–1995) and HAART (1996–1999 and 2000–2005)].

Results: Adjusted prevalences of FRP remained low for CD4 T-cell counts >400 cells per cubic millimeter and increased exponentially and significantly for lower counts. Results were unaffected by

treatment era. After 1996, CD4 T-cell count, but not plasma viral load, was independently associated with FRP.

Conclusions: CD4 T-cell count predicted the development of a FRP among HIV-infected men, independent of HAART use. This suggests that compromise of the immune system in HIV-infected individuals contributes to the systemic physiologic dysfunction of frailty.

Key Words: aging, CD4 T-cell count, frailty, highly active antiretroviral therapy, HIV, prospective population-based cohort

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INTRODUCTION

Similarities in immune dysfunction between aging and HIV infection have been noted.^{1–3} Aging is associated with lymphopenia and a progressive deficiency of CD4 T cells.^{4,5} An increase in the subset of CD8 T cells not expressing CD28 (CD8⁺CD28⁻) and the shortening of telomeres of these cells are hallmarks of immunosenescence.⁶ Such changes have also been observed during HIV infection.^{7,8} It has been hypothesized that a low total lymphocyte count, which is a marker of advancing HIV infection,⁹ may also be a marker of a general decline in physiological functions among healthy elderly individuals.¹⁰

Although aging is associated with increased risk of specific diseases, it is also associated with development of frailty, often not in association with any specific disease.^{11–14} Rather, frailty is a syndrome^{15–17} that involves enhanced vulnerability to stressors and is thought to be due to multisystem dysregulation.^{17–19} It has a clinical phenotype of loss of muscle mass and decreased energy and reserves, with resulting weight loss and declines in strength, exercise tolerance, performance speed, and physical activity,^{16,17,19} and is predictive of mortality and loss of independence.^{15,16} Potential etiologic factors of frailty such as inflammation, oxidative stress, and endocrine and immune dysfunctions^{21–27} have also been encountered in HIV infection.^{28–32} It is not known if these factors are related to frailty in HIV-positive individuals,³³ as they are during aging in the absence of HIV. However, the phenotype of frailty is remarkably similar to the wasting syndrome that occurs in HIV infection,^{34–36} which is an AIDS-defining illness.³⁷

We recently showed that the prevalence and duration of HIV-1 infection were associated with a frailty-like phenotype

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From the *Department of Epidemiology; and †Department of Molecular Microbiology and Immunology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD; ‡Division of Geriatric Medicine and Gerontology and Center on Aging and Health, Johns Hopkins School of Medicine, Baltimore, MD; §Howard Brown Health Center and Department of Medicine, Northwestern University, Chicago, IL; ||Department of Medicine, Geffen School of Medicine, UCLA Medical Center, University of California, Los Angeles, CA; and ¶Department of Infectious Diseases and Microbiology, University of Pittsburgh, Pittsburgh, PA.

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The MACS website is located at <http://www.statepi.jhsph.edu/macs/mac.html>.

Correspondence to: Loic Desquilbet, PhD, Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, 615 North Wolfe Street, Room E7644, Baltimore, MD 21205 (e-mail: desquilbet@agroparistech.fr).

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in the absence of potent antiretroviral therapy.³⁸ Further, the onset of a wasting syndrome indicates a poor prognosis among HIV positives.^{39,40} These findings support the observation that people with HIV infection and frail HIV-uninfected older adults can have similar clinical presentations⁴¹ and similar risks for mortality.⁴² To the extent that the etiologies of frailty are also similar in both populations, it would provide new insights into the etiology of frailty associated with aging—or perhaps other associated diseases such as cancer or congestive heart failure—and potential therapeutic interventions, for example, therapies targeted to improving anti-inflammatory or immune homeostasis.

In the present study, we sought to provide evidence for a causal relationship between physiologic dysfunction in HIV infection and a frailty-related phenotype (FRP). Specifically, we hypothesized that viral load and its adverse effects on CD4 T-cell count would predict the occurrence of frailty in HIV-positive patients and that the prevalence of both low CD4 counts and frailty would be reduced by highly active antiretroviral therapy (HAART). To address these hypotheses, we examined the prevalence of a FRP in the Multicenter AIDS Cohort Study (MACS), which includes HIV-positive men followed prospectively, with both CD4 T-cell counts and viral load in both the pre-HAART and HAART eras.

METHODS

Study Population

The MACS is an ongoing prospective study of the natural and treated histories of HIV infection. The MACS enrolled 4954 HIV-negative and HIV-positive homosexual men in 1984–1985, 668 in 1987–1991, and 1350 in 2001–2003 in sites located in Baltimore, Chicago, Los Angeles, and Pittsburgh. Participants were then followed every 6 months up to the present. Detailed descriptions of the MACS have been published.^{43–45} Informed consent was obtained from all participants in compliance with the appropriate ethical committee at each study site. Study design and questionnaires are available at: <http://www.statepi.jhsph.edu/mac/mac.html>.

Study participants returned every 6 months for study evaluations that include a standardized interview, physical examinations, questionnaires (including SF-36⁴⁶ and items of the Centers for Epidemiologic Studies Depression Scale⁴⁷), and collection of blood for laboratory testing and storage in local and national repositories.⁴⁸ T-lymphocyte subsets were measured at each MACS center using a standardized flow cytometry protocol. Levels of plasma HIV RNA (viral load) were measured using either the standard reverse transcription–polymerase chain reaction assay (level of detection = 400 copies/mL; Roche Diagnostics, Nutley, NJ) or with the Roche ultrasensitive assay (level of detection = 50 copies/mL; Roche Diagnostics). Retrospective testing of stored plasma was performed for selected men using the same assays. HIV seropositivity was determined by a positive enzyme-linked immunosorbent assay confirmed by Western blot. HAART was defined according to the US Department of Health and Human Services Kaiser Panel guidelines⁴⁹ as (1) 2 or more nucleoside reverse transcriptase inhibitors (NRTIs) in combination with at

least 1 protease inhibitor (PI) or 1 nonnucleoside reverse transcriptase inhibitor (NNRTI), (2) 1 NRTI in combination with at least 1 PI and at least 1 NNRTI, (3) a regimen containing ritonavir and saquinavir in combination with 1 NRTI and no NNRTIs; and (4) an abacavir-containing or tenofovir-containing regimen of 3 or more NRTIs in the absence of PIs and NNRTIs. Combinations of zidovudine and stavudine with a PI or a NNRTI were not considered HAART. Therapy regimens not classified as HAART were categorized as either monotherapy or combination antiretroviral therapy.

Study Outcome

The main outcome was the presence of a FRP, as previously defined among the HIV-negative men enrolled in the MACS³⁸ to approximate the phenotypic definition of frailty proposed by Fried et al.¹⁶ This phenotype is based on measurements of 5 components: weakness (grip strength), slowness (time to walk 15 feet), exhaustion (self-reported), low physical activity level (measured through a weighted score of kilocalories expended per week), and weight loss (self-reported). To assess the FRP (see below), we utilized data collected in the MACS that reflect 4 of these components, including the SF-36 quality of life questionnaire,⁵⁰ which was implemented in the MACS in April 1994 (visit 21). The FRP was identified using 1 item selected from the questionnaires for each of the following 4 components: weight loss (answer “yes” to “since your last visit, have you had unintentional weight loss of at least 10 pounds”), exhaustion [answer “yes” to “during the past 4 weeks, as a result of your physical health, have you had difficulty performing your work or other activities (for example, it took extra effort)?”], slowness (answer “yes, limited a lot” to “does your health now limit you in walking several blocks?”), and low physical activity level (answer “yes, limited a lot” to “does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?”). The assessment of weakness (ie, grip strength) was not incorporated into the MACS protocol until October 2005 and therefore could not be used in defining the FRP. A participant was considered as having the FRP at the visit if at least 3 of the 4 components were present. The FRP thus defined had a prevalence of 4.4% among MACS HIV-uninfected men aged 65 years and older,³⁸ which was similar to the prevalence of frailty observed in the Cardiovascular Health Study for men of similar ages.¹⁶

Statistical Analysis

The study population was restricted to all HIV-seropositive men observed from April 1994 (visit 21) through April 2005 (visit 42), which included 1046 men. Logistic regression models were performed using generalized estimating equations (GEE) to adjust for correlated repeated measurements within each individual.⁵¹ The outcome was FRP at each visit, and we specified an autoregressive working correlation matrix and logit link function.

In a first analysis, we assessed the independent effects of CD4 T-cell count and plasma viral load on the prevalence of the FRP during the HAART era. Three multivariate models (models A–C) were performed. Besides potential confounders, model A included CD4 T-cell count, model B included plasma

viral load, and model C included both variables. Potential confounders were age, ethnicity (white non-Hispanic versus other), education (college or higher versus lower), and presence or absence of a clinical AIDS diagnosis. The values for CD4 T-cell count, plasma viral load, age, and clinical AIDS were the ones recorded at the previous visit, whereas the outcome was the FRP recorded at the current visit. Each visit was considered as an “AIDS visit” if it occurred later than 6 months before the first AIDS-defining illness (ie, if the visit occurred after the date of the first AIDS-defining illness minus 6 months), defined according to the 1993 Centers for Disease Control and Prevention definition except that a CD4 T-cell count <200 cells per cubic millimeter by itself was not considered AIDS.³⁷ Fractional polynomials with a power of 1/2 were used for CD4 T-cell count to allow a flexible curve to be fitted to dose-response data.⁵² Because 50% of the viral load measurements were ≤400 copies per milliliter, it was not possible to analyze this variable as continuously distributed. Therefore, we categorized viral load into 3 following indicator variables: ≤400 copies per milliliter (50% of the measurements), 401–50,000 copies per milliliter (39%), and >50,000 copies per milliliter (1%).

In a second analysis, we evaluated the effect of HAART on the FRP by using a population-based approach using calendar time as an instrumental variable, rather than an individual-based approach. This approach has been used to assess the effectiveness of HAART on time to AIDS and death.^{53,54} Three indicator variables were assigned according to calendar periods as follows: pre-HAART (1994–1995), introduction of HAART (1996–1999), and established HAART (2000–2005) eras; the multivariate GEE model included the first 2 indicator variables, CD4 T-cell count modeled as in the first analysis, and the potential confounders cited above. Plasma viral load was not incorporated into the model because of insufficient data during the pre-HAART era.

To evaluate the effect of missing data on estimates of factors associated with FRP status, multiple imputations⁵⁵ were used to check the validity of the results. The Markov chain Monte Carlo method was used to impute values for each of 5 data sets ($m = 5$) with an arbitrary missing pattern, assuming a multivariate normal distribution for the data. SAS procedure MI was performed to impute values for each of the 4 FRP-related components when missing, using information at each visit on: income, employment status, education, smoking status, biological markers (viral load; and CD4, CD8, and CD3 T-cell counts), age, and current use of HAART.

The cutoff date of the study was the April 30, 2005. Stata software V9.0 (Stata Corp, College Station, TX) was used to determine the power of the fractional polynomials. SAS V9.1 (SAS Institute, Cary, NC) was used for the GEE models (procedure GENMOD) and multiple imputation analysis (procedure MIANALYZE).

RESULTS

Description of the Study Population and Person-Visits

The study population consisted of 1046 HIV-positive men who were enrolled in the MACS before 1996 and who

contributed 13,731 person-visits between April 1994 and April 2005. Nine hundred forty-one, 835, and 741 men contributed at least 1 person-visit in the 1994–1995, 1996–1999, and 2000–2005 eras, respectively. The vast majority of these men were white non-Hispanic, and the majority were college educated (Table 1). The median age in 1994 was 39 years, with an age range of 22–65, and the median seropositive time contributed in the analytical period (April 1994 to April 2005) was 9.2 years.

Of the 13,731 person-visits, the FRP could be evaluated in 12,530 (91%) person-visits. Of the 1201 nonevaluable cases, 95% resulted from missing quality of life data; these were evenly distributed across the 3 study eras (data not shown). Table 2 describes the 12,530 person-visits with evaluable FRP status according to the 3 eras defined above. The overall unadjusted prevalence of FRP decreased from 7.6% in 1994–1995, when approximately a quarter of visits were under monotherapy and the majority were not under treatment, to 4.5% in 2000–2005, when approximately 80% of the men were under treatment, almost all of which was HAART. The median number of CD4 T cells increased from 323 to 494 cells per cubic millimeter and the median age from 41 to 48 years.

To determine the independent influence of AIDS on the prevalence of FRP, we excluded person-visits occurring later than 6 months before the first AIDS-defining illness (Table 2). Among AIDS-free person visits, the prevalence of the FRP was around 3% in 1994–1995, 1996–1999, and 2000–2005. However, among person-visits occurring later than 6 months before the first AIDS-defining illness, for example, in the presence of AIDS, the prevalence of FRP decreased by more than half (from 24.0% to 10.1%) after the advent of HAART therapy.

Risk Factors for the FRP in the HAART Era (1996–2005)

In univariate analysis (unadjusted models), having an AIDS-defining illness was significantly associated with an increased risk of FRP, as were older age, white non-Hispanic

TABLE 1. Demographic Characteristics of HIV-Seropositive Men Followed in the MACS Between Visit 21 (April to September 1994) Through Visit 42 (April to September 2005)

Variables	n = 1046 HIV+ Men
White non-Hispanic % (n)	80 (835)
≥College % (n)	52 (548)
No. CD4 T-cell measurements*†	13 (4–20)
Follow-up time (yrs)*†	9.2 (3.0–10.5)
Age at January 1, 1994*	39 (35–44)
Year of 1st clinical AIDS diagnosis % (n)	
Before 1996	25 (265)
1996–1999	11 (115)
2000–2004	3 (33)
Never	61 (633)

*Median (interquartile range).

†From first HIV+ visit (≥visit 21, April 1994) through last visit.

TABLE 2. Description of Person-Visits by Era

Variables	Characteristics According to Calendar Period			Overall (N = 12,530)
	1994–1995 (n = 2459)	1996–1999 (n = 4891)	2000–2005 (n = 5180)	
Overall person-visits % (n)				
FRP	7.6 (186)	5.2 (255)	4.5 (232)	5.4 (673)
Current age*	41 (37–46)	43 (39–48)	48 (43–52)	45 (40–50)
Clinical AIDS person-visits†	20.7 (509)	20.2 (986)	21.7 (1126)	20.9 (2621)
Current CD4 T-cell count (cells/mm ³)*	323 (140–503)	415 (262–609)	494 (329–704)	431 (268–632)
Current viral load (log ₁₀ copies/mL)	NA	3.2 (<1.6–4.3)	<1.6 (<1.6–3.6)	3.0 (<1.6–4.3)
Type of current treatment % (n)				
Not treated	57.7 (1403)	25.5 (1226)	19.8 (1014)	29.4 (3643)
Monotherapy	26.1 (634)	3.4 (181)	0.9 (47)	7.0 (862)
Combination therapy	16.2 (393)	18.8 (904)	10.6 (545)	14.9 (1842)
HAART	<0.1 (2)	52.0 (2526)	68.7 (3520)	48.7 (6028)
Person-visits without clinical AIDS % (n)				
FRP	3.3 (64)	2.4 (95)	2.9 (118)	2.8 (277)
Current age*	41 (36–46)	43 (39–48)	48 (43–52)	45 (40–50)
Current CD4 T-cell count (cells/mm ³)*	390 (237–551)	457 (306–650)	521 (361–739)	467 (314–667)
Person-visits with clinical AIDS % (n)				
FRP	24.0 (122)	16.2 (160)	10.1 (114)	15.1 (396)
Time from AIDS diagnosis (yrs)*	0.9 (0.2–2.3)	2.6 (1.2–4.3)	6.5 (4.3–8.8)	3.6 (1.4–6.6)
Current age*	41 (37–45)	43 (40–48)	48 (44–52)	45 (41–50)
Current CD4 T-cell count (cells/mm ³)*	51 (16–173)	251 (126–395)	378 (235–582)	265 (108–451)

*Median (interquartile range).

†Person-visits occurring within 6 months before a clinical AIDS diagnosis and thereafter.

ethnicity, and low education (<college) (Table 3). Of note, after excluding visits where the AIDS-defining illness was the wasting syndrome, the odds ratio for the association of FRP with AIDS was still significantly elevated at 4.23 [95% confidence interval (CI), 3.00 to 5.96; $P < 0.01$]. A lower CD4

T-cell count was highly, and significantly, predictive of onset of FRP at the subsequent visit. Finally, men with a plasma viral load level >50,000 copies per milliliter were more likely to manifest the FRP than men with a plasma viral load level ≤ 400 copies per milliliter ($P < 0.01$), whereas a plasma viral

TABLE 3. ORs of Having the FRP Among HIV-Seropositive Men Followed in the MACS Cohort Between January 1, 1996 and April 30, 2005

Exposures	OR [95% CI]			
	Unadjusted Models	Adjusted Model A	Adjusted Model B	Adjusted Model C
<College versus \geq college	1.54 (1.09 to 2.17)*	1.75 (1.22 to 2.51)†	1.74 (1.21 to 2.51)†	1.73 (1.19 to 2.50)†
White non-Hispanic versus other	1.62 (1.06 to 2.49)*	1.29 (0.83 to 2.00)	1.28 (0.81 to 2.01)	1.30 (0.82 to 2.06)
AIDS visit versus AIDS-free visits‡	4.83 (3.51 to 6.65)†	3.63 (2.55 to 5.16)†	4.97 (3.53 to 7.01)†	3.62 (2.50 to 5.24)†
Age ($\times 10$ yrs)	1.44 (1.19 to 1.75)†	1.48 (1.21 to 1.80)†	1.54 (1.25 to 1.90)†	1.52 (1.24 to 1.87)†
Plasma viral load (in copies/mL)				
≤ 400	1	—	1	1
401–50,000	1.03 (0.78 to 1.37)	—	1.21 (0.89 to 1.64)	0.98 (0.71 to 1.35)
>50,000	1.72 (1.26 to 2.34)†	—	1.90 (1.37 to 2.63)†	1.09 (0.74 to 1.61)
CD4 T-cell count (in cells/mm ³)				
100	3.65 (2.79 to 4.77)†	2.84 (2.11 to 3.83)†	—	2.80 (1.97 to 3.98)†
200	2.36 (1.98 to 2.83)†	2.00 (1.64 to 2.44)†	—	1.98 (1.57 to 2.50)†
350	1.47 (1.35 to 1.59)†	1.36 (1.25 to 1.49)†	—	1.36 (1.22 to 1.50)†
500	1	1	—	1
750	0.59 (0.53 to 0.66)†	0.65 (0.58 to 0.74)†	—	0.66 (0.57 to 0.76)†

OR, odds ratio.

* $P \leq 0.05$.† $P \leq 0.01$.

‡AIDS visit = visit occurring later than 6 months before the first AIDS-defining illness.

load level of 40–501,000 copies per milliliter was not significantly associated with a higher prevalence of the FRP ($P = 0.81$).

To assess the independent associations of viral load and CD4 T-cell count with the presence of the FRP, we utilized 3 multivariate models (Table 3) incorporating either CD4 T-cell count (model A), viral load (model B), or both (model C). Both a low CD4 T-cell count and a high plasma viral load were significant predictors individually. However, viral load was not significantly associated with the FRP in the model that included CD4 T-cell count (model C), and the effect of the CD4 T-cell count was not attenuated. In model C, the effect of having an AIDS-defining illness, a low education, and an increasing age also remained essentially unchanged from the model with CD4 T-cell count (model A). The independent association of AIDS with FRP persisted even after excluding visits in which an individual manifested the wasting syndrome [adjusted odds ratio (aOR), 3.34; 95% CI, 2.24 to 4.94; $P < 0.01$]. Of note, there was no significant interaction between CD4 T-cell count and either age, AIDS, or viral load. Because of the potential for control of viremia without full reconstitution in CD4 T-cell count, we evaluated whether the association of CD4 T-cell count with FRP persisted among treated patients who controlled HIV replication. For this analysis, we selected person-visits where patients were treated with HAART and where HIV RNA <400 copies per milliliter and found that the association of CD4 T-cell count with the FRP was essentially unchanged (aOR of 2.69 for men with 100 cells/mm³ versus 500 cells/mm³; 95% CI, 1.71 to 4.24; $P < 0.01$). Further adjustment for the presence of chronic hepatitis B or C or depressive symptoms (based on the Centers for Epidemiologic Studies Depression scale) did not substantially affect the association of the CD4 T-cell count with the FRP (data not shown). Hepatitis B or C status was not associated with the FRP, whereas men with moderate depressive symptoms (scores of 16–21; aOR, 2.40; 95% CI, 1.71 to 3.37; $P < 0.01$) and men with severe depressive symptoms (scores ≥ 22 ; aOR, 3.59; 95% CI, 2.55 to 5.05; $P < 0.01$) had higher risks for manifesting the FRP than the other men (scores < 16).

Relationships Between the FRP and CD4 T-Cell Count in Pre-HAART and Current HAART Eras (1994–2005)

Figure 1 displays the relationship between CD4 T-cell count and the estimated prevalence of FRP according to the 3 calendar periods, for age fixed at 45 years and for values of ethnicity, education, and AIDS fixed at the average of the study population. There was no significant interaction between CD4 T-cell count and calendar period. Therefore, the shapes of the relationships between CD4 T-cell count and estimated prevalence of FRP were similar in all eras. However, after adjustment for age, CD4 T-cell count, clinical AIDS status, education, and ethnicity, the overall prevalence of FRP was higher in the pre-HAART era (1994–1995) than in both the introduction of HAART (1996–1999) (aOR, 1.47; 95% CI, 1.16 to 1.86; $P < 0.01$) and established (2000–2005) HAART eras (aOR, 1.56; 95% CI, 1.15 to 2.11; $P < 0.01$), whereas the prevalence of FRP was similar in the introduction of HAART

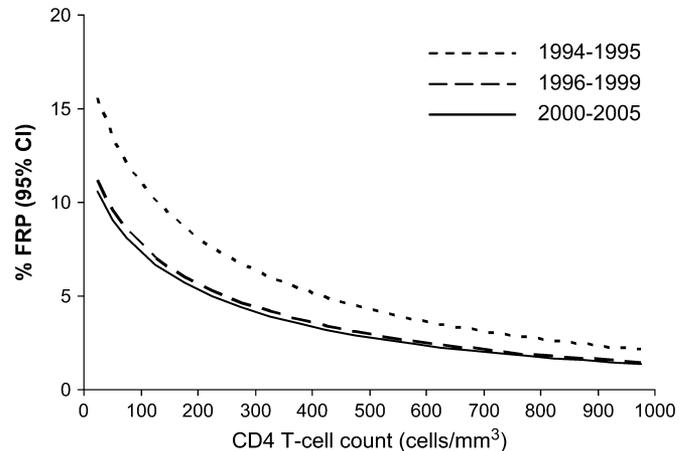


FIGURE 1. Estimated prevalences of a FRP as a function of CD4 T-cell count in the MACS for fixed values of age (45 years), fixed percentage for ethnicity (80% white non-Hispanic), education (52% \geq college), and prevalence of AIDS (20%), in the pre-HAART era (1994–1995; dotted line), introduction of HAART era (1996–1999; dashed line), and established HAART era (2000–2005; plain line). The curves for the 2 HAART eras do not differ significantly from each other, but both are significantly different from that of the pre-HAART era (see text for odds ratios and P values comparing the 3 different eras).

era compared with established HAART era (aOR, 1.06; 95% CI, 0.82 to 1.37; $P = 0.64$).

To estimate the potential impact of missing data on predictors of FRP (8.8% of the 13,731 person-visits), a 5-set multiple imputation analysis was carried out. Estimates and standard errors calculated from the multiple imputation model remained essentially unchanged from those provided in the above analysis (data not shown).

DISCUSSION

This study extends a previous report in which we defined a FRP³⁸ to approximate the clinical definition of a frailty phenotype by Fried et al¹⁶ and showed it to be associated with HIV-1 infection.³⁸ In the present study, a low CD4 T-cell count was an independent significant predictor of the FRP in HIV-positive men, adjusting for AIDS, and also in the absence of having a wasting syndrome. Furthermore, the association between CD4 T-cell count and the FRP remained the same after restriction to HAART-treated men with a good virological response to HAART (whether they had a CD4 cell response or not) or after taking into account hepatitis B or C status and depressive symptoms. These findings provide evidence that the FRP is etiologically related to a compromised immune system as associated with HIV infection. Of note, the findings of the present study parallel other work in older HIV-uninfected individuals which indicates that a compromised immune system is associated with frailty and predictive of mortality.^{27,56–58} Taken together, these findings support the notion of a common etiology of frailty associated with aging and with HIV.

The finding that the prevalence of FRP declined by about 50% from the pre-HAART to the HAART era provides

the first evidence that improvement of immune function can reduce the development of a frailty-like presentation. One explanation for this result might be decreased immune activation due to suppression of viral replication and viremia. Another explanation might be the psychological positive impact of the introduction of HAART in the HIV population,^{59,60} which could have reduced the onset of frailty through an increase in mental health and/or physical activity.¹⁹ Whatever the mechanism, this observation has important implications for potential prevention of frailty in aging and in HIV infection.

Of note, we estimated that in the current HAART era, the impact of a 10-year increase in age was similar to that of a decrease of 250 CD4 T cells per cubic millimeter for average ages and CD4 T-cell counts. Even at relatively high CD4 T-cell counts, deterioration of the immune system conferred an effect similar to that associated with aging in increasing the risk of developing the FRP. These data are consistent with an important role of the immune system in the aging process, and specifically in frailty,²⁵ although the specific relationship between CD4 T-cell counts and the aging-related outcome described here would not necessarily be expected to pertain to HIV-uninfected populations. Frailty is a late-stage clinical syndrome that in older adults is hypothesized to result from dysregulation or failure of many physiological systems.^{17–20} It is of import that this report indicates that widespread use of HAART in HIV-infected persons was associated with an overall decrease in the prevalence of the FRP. This suggests that immunotherapy could have a role in the prevention or treatment of frailty in aging, even though it directly targets only 1 of the many systems likely to be dysregulated in frailty. To clarify the import of the decrease in FRP associated with HAART, it will now be important to determine whether frailty in HIV infection is a predictor of vulnerability to adverse outcomes, including mortality, as it is in aging in the absence of HIV infection, and if so whether this is independent of immune compromise and other consequences of HIV infection. Our preliminary analyses suggest that this is indeed the case (⁴², unpublished data).

We observed that among AIDS-free men, the prevalence of FRP remained stable across calendar periods. One explanation for this finding could be that the negative impact of age is balanced by the positive impact of the increase in CD4 T-cell count due to HAART. Conversely, among men with clinically defined AIDS, the prevalence of the FRP strongly decreased between 1994–1995 and 2000–2005. The difference between the responses of men with and without AIDS probably reflects the greater increase in CD4 T-cell count induced by HAART in the former group compared with the latter group (Table 2). After adjustment for ethnicity, education, and AIDS status, we found that the prevalence of the FRP decreased with the introduction of HAART but did not decrease further as the HAART era progressed. This result is consistent with the finding that the CD4 T-cell count increases primarily within the first 2 years after HAART initiation.⁶¹

Several findings from the present study may be important for both HIV and frailty research. First, the nonlinear association between the prevalence of the FRP and CD4 T-cell count suggests that in HIV-infected men, there may be

a threshold CD4 T-cell level at which the FRP develops or becomes manifest. Second, in the HAART era, men with a high viral load (>50,000 copies/mL) did not manifest the FRP more frequently than those with low viral load (<400 copies/mL) after adjustment for age and CD4 T-cell count. This is consistent with the idea that the presence of FRP may be on the same causal pathway as viral load and its effect on CD4 T-cell count, but related more closely to the CD4 T-cell count itself, as discussed above. Alternatively, we may not have had the power to detect an association with viral load because only 11% of viral load measurements were above 50,000 copies per milliliter. However, the large decrease in the point estimate for this category after adjusting for CD4 T-cell count argues against this explanation. Third, the prevalence of FRP decreased since the introduction of HAART independently of CD4 T-cell count, which implies that the effect of HAART is not fully mediated through the increase in CD4 T-cell count.

Anemia and comorbidities such as chronic renal disorders have been shown to be associated with frailty in the elderly HIV-uninfected population^{62,63} and also with HIV infection.^{64,65} These factors were not included in this analysis because they are likely to be in the causal pathway for the FRP, that is, anemia and chronic diseases might be consequences of the decrease in CD4 T-cell count. Analyzing these factors as if they were confounders would lead to bias and may erroneously attenuate the association between CD4 cell count and frailty.⁶⁶

This study has some limitations. First, we studied a frailty-like phenotype rather than the exact frailty phenotype previously defined and validated.¹⁶ This approach was dictated by the data available in the study. Designed to approximate the frailty phenotype for 4 of 5 validated criteria for defining the frailty phenotype, its likely decreased specificity still yielded meaningful findings. Second, although we looked at the association between FRP at a given visit and CD4 T-cell count and/or viral load at the previous visit using longitudinal prospective data, we cannot conclude from our observational study that CD4 T-cell count (and not viral load) is a causal factor of the occurrence of the FRP. Third, a substantial proportion (8.8%) of person-visits could not be classified as having or not having the FRP. However, the vast majority of these were due to missing quality of life questionnaire data, and the consistency of the results obtained from multiple imputations argues that the amount of bias introduced by missing data, if any, was minimal. Fourth, we used calendar era as an instrumental variable for use of therapy. The close link between availability of HAART, its uptake in the cohort, and calendar time permits the effects of HAART to be examined on the population level as done by others.^{53,54} However, in a given era, not all infected persons utilized the same treatment, nor was HAART a uniform therapeutic regimen. Further analyses are necessary to study the effect of HAART on the manifestation of FRP at the individual level. Finally, our study population was composed of men only, so no inference can be drawn concerning occurrence of frailty in women.

Aging is associated with a decline in immune function and increased inflammatory activity and with increased levels of proinflammatory cytokines such as interleukin 6 and tumor

necrosis factor α .²⁵ In the elderly, elevated interleukin 6 levels have been reported to be associated with physical decline, age-related diseases (such as Alzheimer disease, osteoporosis, cognitive decline), and frailty,^{21,67–70} whereas elevated tumor necrosis factor α levels are believed to be associated with mortality.^{71,72} Several studies have also reported elevated levels of those cytokines in HIV infection.^{73–76} It has also recently been shown that the number of CD8 T cells that have lost expression of the costimulatory receptor CD28 (CD8⁺CD28⁻) was greater among frail elderly women than in their nonfrail counterparts.⁷⁷ This T-cell subset is believed to be a good biological marker of intrinsic aging of the immune system⁷⁸; it is also considered as a marker of immunosenescence resulting from chronic activation of the immune system,^{79,80} where chronic infections such as cytomegalovirus⁸¹ or HIV⁸² may play an important role; indeed, markers of chronic cytomegalovirus infection are associated with frailty.⁸³ In addition to our previous results that suggested that HIV infection might accelerate some manifestations of aging,³⁸ the present study provides biologic plausibility for the hypotheses that frailty is a final common pathway from a variety of processes (eg, chronic diseases and aging), where the secondary immunologic dysfunction seems to be the driver more than the ultimate cause.^{84,85} The evidence of decreased rates of a frailty-like phenotype in the HAART era provides the first evidence of the potential to prevent this predictor of mortality.

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