

HIV-1 Infection Is Associated With an Earlier Occurrence of a Phenotype Related to Frailty

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Background. Older healthy and HIV-infected adults exhibit physiological similarities. Frailty is a clinical syndrome associated with aging that identifies a subset of older adults at high risk of mortality and other outcomes. We investigated whether HIV infection increases the prevalence of a frailty-related phenotype (FRP) that approximates a clinical definition of frailty.

Methods. We first defined the FRP and assessed its prevalence among HIV-uninfected men followed in the Multicenter AIDS Cohort Study (MACS) between 1994 and 2004. Using repeated measurements logistic regression models, we then assessed the association between FRP and HIV infection before the era of highly active antiretroviral therapies, adjusting for covariates among HIV-uninfected ($N = 1905$) and incident HIV cases ($N = 245$).

Results. HIV infection was strongly associated with FRP prevalence. Compared to HIV-uninfected men of similar age, ethnicity and education, HIV-infected men were more likely to have the FRP for all durations of infection: for ≤ 4 years, the adjusted odds ratio (OR) was 3.38, with 95% confidence interval (CI), 1.25–9.11, and for 4.01–8 years and 8.01–12 years the corresponding figures were (OR = 12.95, 95% CI, 6.60–25.40) and (OR = 14.68, 95% CI, 7.60–28.35), respectively. The FRP prevalence for 55-year-old men infected with HIV for ≤ 4 years (3.4%; 95% CI, 1.3–8.6) was similar to that of uninfected men ≥ 65 years old (3.4%; 95% CI, 1.5–7.6).

Conclusion. In this cohort, HIV infection was associated with an earlier occurrence of a phenotype that resembles the phenotype of frailty in older adults without HIV infection. Studies of frailty in the setting of HIV infection may help to clarify the biological mechanism of frailty.

BIOLOGICAL similarities have been noted between aging and HIV infection. Both are associated with DNA damage and loss of repair capability (1,2), neuroendocrine changes (3–5), sarcopenia (6), dysregulation of apoptosis (7,8), and immune changes (9). Among the immunological changes seen in both aging and HIV infection are a progressive loss of CD8 T cells (10,11), an expansion of CD8+CD28–T cells (12,13), and an overall immune deterioration (9,14), although this is much more severe in HIV infection.

Although aging is associated with increased risk of specific diseases, it can also manifest as frailty (15–18), a syndrome that involves enhanced vulnerability to stressors and is thought to be due to dysregulation of multiple physiologic systems (18–20). There is evidence that it predicts loss of independence and death, consistent with geriatricians' observations (19–24). The biologic basis of frailty in the elderly population is unknown, although emerging evidence indicates underlying immunologic and inflammatory dysregulation (25–30) in concert with alterations in multiple other physiologic systems including sarcopenia, anemia, and hormonal impairments (28–34). Additionally,

the clinical presentation of frailty—including loss of muscle mass, weight, and energy; slowed motor performance; and low physical activity—bears strong resemblance to that of the later stages of HIV infection.

Because of the physiologic parallels between aging and HIV infection, and because of clinical parallels in symptoms and signs of frailty (19,21) and HIV infection (35), we hypothesized that HIV infection might be causally associated with a frailty-like clinical presentation. The purpose of the present study, therefore, was to investigate whether HIV infection increases the prevalence of a frailty-related phenotype (FRP) among men followed in the Multicenter AIDS Cohort Study (MACS). The data evaluated were collected before the availability of highly active antiretroviral therapy (HAART), which dramatically alters the progression of HIV disease. We first defined a FRP among the HIV-uninfected members of the MACS to approximate the syndrome of frailty as it has been clinically defined in the elderly population (19,24). We applied this first to the HIV-uninfected members of the MACS, and then investigated whether the prevalence of this phenotype was increased among the HIV-infected members of the cohort compared to those

uninfected, and whether it was associated with duration of HIV infection.

MATERIAL AND METHODS

Study Population

The MACS is an ongoing prospective cohort study designed to assess the natural and treated histories of HIV infection in homosexual men. The cohort enrolled both HIV-infected and uninfected men in Baltimore/Washington, Chicago, Los Angeles, and Pittsburgh in 1984–1985, 1987–1991, and 2001–2003. Men with clinical AIDS prior to treatment or who were younger than 18 years were ineligible for enrollment. The median (interquartile range) ages at the time of enrollment were 32 (28–37), 31 (26–36), and 38 (32–43) years, respectively, for the men enrolled in 1984–1985, 1987–1991, and 2001–2003. Informed consent was obtained from all participants in compliance with the appropriate ethics committees. Study design and questionnaires are available at <http://www.statepi.jhsph.edu/mac/mac.html>. Other details about the recruitment and characteristics of the MACS cohort have been reported elsewhere (36,37).

The participants return every 6 months for study visits that include a detailed interview; a physical examination; interviewer- and self-administered questionnaires on medical history, behavioral practices, and health care utilization; and collection of blood for concomitant laboratory testing and storage in local and national repositories (38). T-lymphocyte subsets were measured by each MACS center using a standardized flow cytometry protocol. Levels of HIV RNA were measured using the standard reverse transcription–polymerase chain reaction assay and, subsequently, with the Roche ultrasensitive assay (level of detection = 50 copies/mL; Roche Diagnostics, Nutley, NJ) if found undetectable at 400 copies/mL. Retrospective testing of stored plasma was performed for selected men using the same assays. HIV seropositivity is determined by a positive enzyme-linked immunosorbent assay (ELISA) and confirmatory Western blot. Diagnoses of AIDS, cancers, and neurological outcomes were confirmed by review of medical records. The self-administered Short Form (SF)-36 quality-of-life questionnaire (39) was incorporated and validated in the MACS protocol as of visit 21 in 1994 (40).

Definition of an FRP

Although there is no single definition of frailty (41–45), Fried and colleagues proposed and validated a phenotypic definition of frailty, based on a theory that the clinical presentation was syndromic and the results of underlying physiologic dysregulations (19,43). This syndromic definition was operationalized as requiring a critical mass of clinical criteria, that is, the presence of at least three of the following five components: physical shrinking (unintentional weight loss), exhaustion (self-reported), low physical activity level (measured through a weighted score of kilocalories expended per week), slowness (time to walk 15 feet), and weakness (grip strength) (19,24). By this definition, the prevalence of frailty among community-dwelling

men in the Cardiovascular Health Study (CHS) (46,47) was ~2% at ages 65–70 years and ~3% at 71–74 years (19).

Although the MACS was not initially designed to evaluate frailty, we sought to define an FRP that could most closely approximate the core clinical presentations of frailty with the data available in the MACS. This approach has also been applied in other studies (23,48). The first three of the five components were ascertained from the MACS database. There was no measurement of weakness, and although there was no direct measurement of slowness, this component was approximated using questions about difficulty in walking various distances (49). Therefore, the FRP was defined by the presence of at least three of the following four components: physical shrinking, exhaustion, slowness, and low physical activity level. To choose the final definition from among the potentially FRP-related items included in the questionnaires, we selected one item per component in three steps. Step 1: We qualitatively selected items as possible approximates of the four components of frailty (content validity, Table 1). Step 2: We (quantitatively) determined that the prevalence of the item increased with age (construct validity). Step 3: The final definition of the FRP was chosen such that prevalences for the HIV-uninfected men increased with age and approximated age-specific prevalences of a frailty phenotype for men at the same age in the CHS (19).

Study Samples

To define the FRP, we used only person-visits provided by men who were HIV-uninfected through November 1, 2004, including pre-seroconversion visits for men who subsequently became infected with HIV. Items from the SF-36 questionnaire, which was begun at visit 21 (April 1994), were used in the FRP definition; therefore, individuals who did not contribute data at or after visit 21 were excluded.

To investigate whether HIV infection and its duration increased the prevalence of the FRP, persistently HIV-uninfected men were compared to those who became infected during the study, with a date of seroconversion (estimated as the midpoint between the last HIV-negative and the first HIV-positive visit) known to within ± 12 months. The analysis was censored at January 1, 1996 for both HIV-uninfected and -infected men to exclude any potential effect of HAART, which dramatically reduced the mortality and morbidity of HIV infection after it became available in 1996 (50).

Statistical Methods

Separate repeated-measures logistic regression models (51) were used to select the optimal MACS questionnaire items to define the FRP. At each visit, the binary outcome was the presence of each of the four components (Step 2), or the FRP (Step 3). Age, categorized into 4-year intervals (from 40 through 65 years), was included in the model through indicator variables. Person-visits at which the FRP could not be defined because of missing data were excluded from the analysis (7.4% of the 12,155 person-visits).

Repeated-measures models were also used for the association between FRP and duration of HIV infection, categorized into 4-year intervals (0 years, 0.01–4 years,

Table 1. List of Items Included in MACS Questionnaires That Qualitatively Approximated Frailty Components and That Were Quantitatively Associated With Age Among HIV-Negative Men From the MACS

Frailty Components (19) and Their Corresponding Items Collected in the MACS	Presence	Absence
Physical shrinking		
“Since your last visit, have you had unintentional weight loss of at least 10 pounds?”* [†]	Yes	No
Exhaustion		
“During the past 4 weeks, as a result of your physical health, have you cut down the amount of time you spent on work or other activities?”	Yes	No
“Since your last visit, have you had persistent fatigue (feeling tired all the time) for at least three consecutive days?”	Yes	No
“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)?”*	Yes	No
Slowness		
“Does your health now limit you in walking more than 1 mile?”	Yes, limited a lot	Yes, limited a little; no, not limited at all
“Does your health now limit you in walking several blocks?”*	Yes, limited a lot	Yes, limited a little; no, not limited at all
Low physical activity level		
“Does your health now limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?”	Yes, limited a lot	Yes, limited a little; no, not limited at all
“Does your health now limit you in bathing or dressing yourself?”	Yes, limited a lot	Yes, limited a little; no, not limited at all
“Does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?”*	Yes, limited a lot	Yes, limited a little; no, not limited at all
Weakness (None were included in the MACS questionnaire)		

Notes: *Items included in final the definition of a frailty-related phenotype.

[†]10 pounds = 4.5 kilograms.

MACS = Multicenter AIDS Cohort Study.

4.01–8 years, or 8.01–12 years [maximum, 11.3 years]) and included as indicator variables. Age was included as a continuous variable. Because most of the study population was white, non-Hispanic, and at least college-educated, ethnicity was dichotomized as white non-Hispanic versus other, and education as college or higher versus less than college. Smoking status (never, former, current use) at enrollment and substance use (hash/marijuana, poppers, cocaine) within 2 years before enrollment were included in subsequent models to take into account potential confounding due to behavioral practices that could differ between HIV-negative and -positive men. The significance of trends by duration of HIV infection was assessed by assigning ordinal dose-specific categories, fitting this variable as a continuous linear term. To illustrate the independent association between FRP, age, and the duration of HIV infection, diamond-shaped equiponderant graphics (52) were used. Statistical analyses were carried out with SAS (version 9.1; SAS Institute, Cary, NC).

RESULTS

Definition and Prevalence of an FRP Among HIV-Uninfected Men

A total of 1977 individuals contributed 12,155 person-visits while HIV-uninfected from April 1, 1994 (visit 21) to November 1, 2004. The median age at January 1, 1994 was 42 years, ranging from 24–79 years (interquartile range [IQR], 37–47 years). In 9% ($n = 1140$) and 4% ($n = 455$) of person-visits, age was ≥ 60 and ≥ 65 years, respectively.

Table 1 lists the items qualitatively selected to approximate each of the four components of an FRP, and whose prevalence increased with age. Because one item had to be chosen, ultimately, for each component of the FRP, there were 18 possible combinations of items that could be chosen to define the phenotype. The items finally selected are indicated in Table 1.

Using this definition, the unadjusted estimates of FRP prevalence increased from 1.0% for men aged 45–49 years to 4.4% for men older than 65 years (Figure 1). In a multivariate model including age, educational level, and ethnicity, the prevalence of the FRP for white non-Hispanic men older than 65 years with an educational level of college or higher was estimated to be 3.4% (95% confidence interval [CI], 1.5–7.6).

The Effect of HIV Infection on the Prevalence of the FRP

A total of 2150 men contributed at least one visit between visit 21 (April 1994) and January 1, 1996 (hereafter called the “study period”). Of these, 1905 were persistently HIV-uninfected and contributed 3966 person-visits, and 245 were HIV-infected, having seroconverted between 1984 and January 1, 1996 (median date of seroconversion, October 1987; range, July 1984–August 1995); 93% and 7% had seroconversion dates known within ± 6 months, and ± 6 –12 months, respectively. These seroconverters contributed 691 person-visits. The seroconverters were younger, less frequently white non-Hispanic, and less likely to have attended college than were HIV-uninfected men (Table 2).

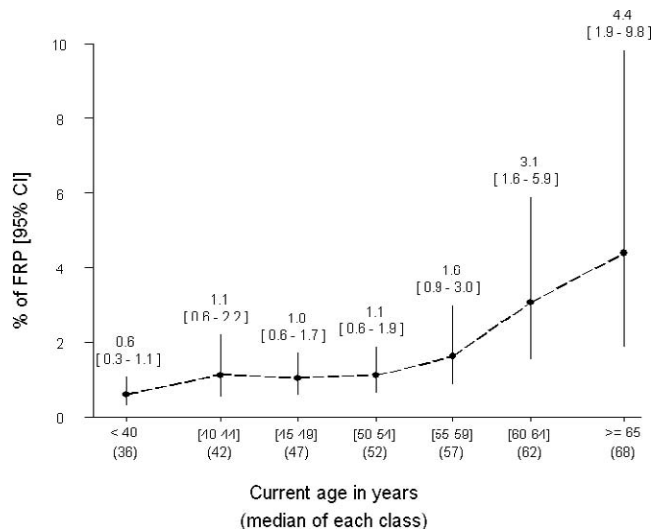


Figure 1. Estimated prevalence of a frailty-related phenotype (FRP) as a function of age among 1977 HIV-seronegative individuals from the Multicenter AIDS Cohort Study (MACS) cohort (April 1994–November 2004) (95% confidence interval [CI]).

They had similar dates of enrollment and distribution across study sites. Among the 245 seroconverters, 35 (14.3%) developed an AIDS-defining illness (53) before visit 21, and 34 (13.9%) between visit 21 and January 1, 1996.

Of the 245 seroconverters, 34 (13.9%) manifested the FRP at least once, as opposed to only 28 (1.5%) of the 1905 HIV-uninfected individuals during the same time period ($p < .01$); in all, the FRP was reported at 50 HIV-positive person-visits and 32 HIV-negative person-visits. We examined whether the FRP was more likely to occur among individuals with comorbidities of cancers and neurological disorders, ascertained according to the standardized MACS protocol. History of a cancer was more frequent among person-visits with FRP than among those free of FRP, in both HIV seropositives (22.0% vs 6.3%; $p < .01$) and HIV seronegatives (6.3% vs 1.6%; $p = .04$). Similar results were observed for neurological disorders for both HIV-positive person-visits (38.0% vs 6.8%; $p < .01$) and HIV-negative person-visits (9.4% vs 1.8%; $p < .01$).

In a multivariate model including age, ethnicity, and educational level (Table 3, Model 1), HIV-infected men were more likely than were uninfected men to manifest physical shrinking (odds ratio [OR] = 12.80), exhaustion (OR = 3.02), slowness (OR = 3.94), low physical activity level (OR = 3.40), and the aggregate FRP (OR = 10.97). Because weight loss is common in HIV infection and was one of the four components of the FRP, we assessed whether these associations remained significant after excluding person-visits at which an unintentional weight loss > 10 pounds (4.5 kilograms) since the last visit was reported. This exclusion did not strongly change associations between HIV infection and the three other frailty components; the association with FRP, although reduced, was still strong and highly significant (Table 3, Model 2; OR = 4.49; $p < .001$).

The risk of exhibiting the FRP increased with duration of HIV infection, after adjusting for age, ethnicity, and education (Table 4 and Figure 2a). Older and college-educated men were more likely to manifest the FRP, although the association with education was of borderline significance. Ethnicity was not significantly associated with FRP. There was no significant interaction between age and duration of HIV infection ($p > .70$), suggesting that these are independent factors; indeed, the effect of duration of HIV infection was observed even at younger ages. The estimated prevalence of the FRP for 55-year-old white non-Hispanic, college-educated men HIV-infected for ≤ 4 years was 3.4% (95% CI, 1.3–8.6), equivalent to the estimate for uninfected men of the same ethnicity and education at age 65 years or older (3.4%; 95% CI, 1.5–7.6).

In additional adjusted models, we found that the prevalence of the FRP was not affected by behavioral practices at enrollment in the cohort such as being a former smoker (OR = 1.21; 95% CI, 0.54–2.75; $p = .64$) or a current smoker (OR = 1.56; 95% CI, 0.87–2.85; $p = .14$) compared to a nonsmoker, or use (compared to non-use) of hash/marijuana (OR = 0.85; 95% CI, 0.47–1.53; $p = .59$), poppers (OR = 0.81; 95% CI, 0.44–1.48; $p = .49$), or cocaine (OR = 1.23; 95% CI, 0.68–2.24; $p = .49$). Adjustments for these behavioral practices did not affect the estimates of the association between the FRP and duration of HIV infection.

Table 2. Demographic Characteristics of HIV-Seronegative Men and Seroconverters Followed in the MACS Cohort Between Visit 21 (April 1, 1994) and January 1, 1996

Characteristics	HIV- (N = 1905)	Seroconverters (N = 245)	p
Date of enrollment*	09/84 (07/84, 12/84)	09/84 (07/84, 12/84)	.84
Age in 1994, y*	42 (37–47)	39 (35–45)	< .01
White non Hispanic, N (%)	1691 (89)	204 (83)	.01
Education level \geq college, N (%)	1238 (65)	128 (52)	< .01
Study center, N (%)			
Baltimore	522 (27)	65 (26)	
Chicago	420 (22)	57 (23)	
Pittsburgh	486 (26)	55 (23)	
Los Angeles	477 (25)	68 (28)	.65

Notes: *Median (interquartile range).

MACS = Multicenter AIDS Cohort Study.

Table 3. Adjusted OR Values for HIV-Infected Versus HIV-uninfected Men to Manifest Each of the Four Components of the FRP and the FRP Overall, in the MACS Between April 1, 1994, and January 1, 1996

PV Analyzed*	Frailty Component								FRP [†]	
	Physical Shrinking		Exhaustion		Slowness		Low Physical Activity Level			
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
All PV	12.80	8.34, 19.64	3.02	2.30, 3.96	3.94	2.37, 6.53	3.40	2.49, 4.64	10.97	6.37, 18.88
PV without weight loss	—		2.24	1.66, 3.01	2.85	1.56, 5.21	2.54	1.79, 3.59	4.49	1.98, 10.19

Notes: All *p* value were < .01.

*For each of the two analyses, five models were performed: one model per component, and one model for the FRP. Each model was adjusted for age, ethnicity, and educational level.

[†]An FRP was present if ≥3 frailty components were present.

PV = person-visits; OR = odds ratio; CI = confidence interval; FRP = frailty-related phenotype; MACS = Multicenter AIDS Cohort Study.

Among HIV-positive individuals and after adjustment for age, ethnicity, and education level, OR values for the presence of the FRP were significant for low (<350 cells/mm³ vs ≥350 cells/mm³) CD4 T-cell count (OR = 2.75; 95% CI, 1.43–5.28), high (≥50,000 copies/mL vs < 50,000 copies/mL) plasma HIV RNA concentration (OR = 2.91; 95% CI, 1.08–7.85), and presence of clinically defined AIDS (53) (OR = 9.89; 95% CI, 4.70–20.80). To determine whether AIDS explained the increased rates of the FRP among the HIV-infected men, and if the FRP emerged in the pre-AIDS phase, we examined the association of FRP with duration of HIV infection excluding person-visits occurring later than 6 months before the first AIDS-defining illness. Duration of HIV infection remained strongly associated with FRP, as did age (Table 4 and Figure 2b); education was of borderline significance. Further supporting the distinction between AIDS and the FRP, we found that of the 34 AIDS cases occurring during the study period, 23 (68%) did not exhibit the FRP during the study period. Of the 32% who did exhibit the FRP during the study period, 3 (9%) had an FRP prior to their first AIDS diagnosis (all within 6 months prior to the diagnosis) and 8 (23%) exhibited the FRP after their AIDS diagnosis.

DISCUSSION

In this study, both HIV infection and AIDS were predictors of frailty-like manifestations, and the duration

of HIV infection was associated with the likelihood of these manifestations. The observed increases of FRP with low CD4 T-cell count and high HIV viral load, two biomarkers of HIV disease progression, suggest a common underlying biology between frailty and HIV disease. However, the presence of the FRP was far from automatic in men with HIV or AIDS. Finally, in this study, HIV infection for ≤4 years appeared to confer a rate of FRP comparable to that of HIV-uninfected men 10 years older, and this rate was further increased by 2- to 3-fold for men infected > 4 years and an additional 2-fold for men with AIDS.

It has been posited that HIV infection demonstrates similarities to aging and possibly to frailty (54). Specifically, HIV infection is associated with diverse impairments that resemble frailty, such as myopathy, loss of muscle mass and weight, fatigue, functional impairments, cognitive dysfunctions and motor abnormalities, as well as rheumatological disorders and neuropathies, even in the absence of identifiable opportunistic illnesses (35). The hypothesis that similar mechanisms operate in aging, frailty, and HIV infection is supported by laboratory data. For example, each exhibits elevated serum concentrations of the proinflammatory cytokine interleukin 6 (IL-6) (55–57). In normal aging, elevated serum levels of IL-6 have been associated with such diseases of later life as loss of muscle mass, loss of mobility, or onset of disability (58,59); cognitive decline (60); and lymphoproliferative disorders, osteoporosis, and Alzheimer’s disease (61). Elevated IL-6 has also been

Table 4. Factors Associated With the Presence of an FRP Among HIV-Seronegative Men and Seroconverters in the MACS Between April 1, 1994, and January 1, 1996

Variables	Including All Person-Visits			Excluding AIDS-Related Person-Visits*		
	OR [†]	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Age (for a 10-y increase)	1.61	1.21, 2.15	< .01	1.53	1.11, 2.11	< .01
White non-Hispanic (vs other)	0.61	0.28, 1.37	.23	0.75	0.26, 2.18	.60
≥College (vs < college)	0.59	0.34, 1.04	.07	0.52	0.26, 1.02	.06
Duration of HIV infection						
0 y	1			1		
0.01–4 y	3.38	1.25, 9.11	< .01 [‡]	2.42	0.78, 7.53	< .01 [‡]
4.01–8 y	12.95	6.60, 25.40		4.17	1.52, 11.45	
8.01–12 y	14.68	7.60, 28.35		6.25	2.30, 16.95	

Notes: *AIDS-related person-visits are person-visits occurring later than 6 months before the first AIDS-defining illness.

[†]Adjusted for all the variables listed in the table.

[‡]Test for trend.

FRP = frailty-related phenotype; MACS = Multicenter AIDS Cohort Study; OR = odds ratio; CI = confidence interval.

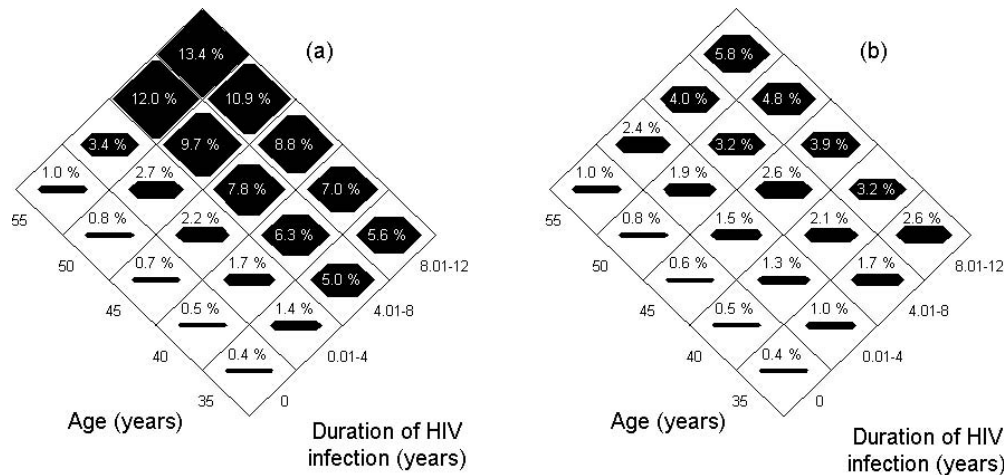


Figure 2. Adjusted prevalence of having a frailty-related phenotype according to age and presence and duration of HIV infection, for fixed values of ethnicity (white non-Hispanic) and educational level (\geq college), among HIV-seronegative and -seroconverted men in the Multicenter AIDS Cohort Study (MACS) between April 1994 and January 1, 1996 when (a) all person-visits were included and (b) excluding person-visits occurring later than 6 months before the first AIDS-defining illness. The ratio of the areas (and middle vertical length) of any two shaded polygons equals the ratio of the two corresponding prevalences written in their centers. For example, the area corresponding to a prevalence of 1.7% is equal in a and b, and is the equivalent of half the area corresponding to a prevalence of 3.4%. See reference (52) for further details.

associated with the frailty syndrome (62). Consequently, it has been hypothesized that IL-6 may causally contribute to the aging process (56,63,64) and/or to the syndrome of frailty (62). In HIV infection, IL-6 levels are also elevated, and the degree of elevation correlates with disease stage (65). It remains to be seen whether frailty in aging and HIV infection will have similar or overlapping mechanisms. However, this study supports such a hypothesis. It is interesting to speculate that impaired immune regulation, which is present in both of these conditions, can predispose to frailty and thus to decreased survival.

Frailty has been shown to be associated with cardiovascular diseases, congestive heart failure, cancer, and chronic infection (19,26,66,67) such as with cytomegalovirus (68,69), although causal relationships are yet to be demonstrated. Our findings, in concert with these data, add weight to the prior hypothesis (19,43) that frailty manifestations could be a final common pathway of diseases associated with wasting syndromes. The strong associations between frailty and mortality previously reported (19–24) offer the inference that the onset of frailty in the presence of these diseases may mark those individuals who are at such high risk. In this connection, we have separately presented evidence that in our cohort of men with HIV infection, presence of the FRP at initiation of HAART is associated with a less favorable response to HAART (70).

It has been difficult to study mechanistically the relationships between HIV infection and aging-related phenotypes because of the complexity of both aging and HIV disease, and because much data on HIV has been collected in young populations and/or prior to the validation of a frailty phenotype. The development and validation of clinical criteria for the recognition of aging-associated frailty (19,24) provided an opportunity to quantitatively explore the degree to which progression of HIV disease might resemble frailty and whether such a resemblance, if present, was due to

opportunistic illnesses or to HIV infection directly. The MACS has particular strengths for such an evaluation, including long follow-up of individuals into older ages, and a large number of HIV-uninfected men similar in age and lifestyle exposures to the HIV-infected men. In contrast, retrospectively in the MACS, it was possible, at best, to approximate only 4 of the 5 criteria for aging-associated frailty. We used these data to assemble an approximate definition of an FRP, not to modify the clinical criteria for frailty previously validated (19); we termed this approximation an FRP (i.e., rather than frailty) specifically to emphasize that we were not redefining the condition. Nevertheless, this approximation showed a strong association with the presence and duration of HIV infection, suggesting a basis for further work in this area. Based on these results, we are now measuring grip strength and walking speed directly in the MACS, in order to have more precise assessment of frailty in the future.

Due to practical limitations, the FRP utilized in this work was selected from data available in the MACS in order to provide a first test of the hypothesis of a relationship between HIV and frailty. The phenotype measures were selected based on a priori expectations that they lead to age-specific prevalences comparable to those seen in the CHS. Furthermore, the apparent curvilinear increase in rates of the FRP with age is consistent with predictions that the aggregation of system impairments with aging would lead to an exponential increase (20,42,71,72). This consistency with predictions leads to improved validity, but also to limitations in drawing inferences about prevalences observed with aging. The associations of FRP with prior cancer and neurologic conditions give credence to the validity of this construct.

Our estimates of frailty are preliminary, for two reasons. First, we studied an FRP rather than the exact frailty phenotype previously defined (19). Second, the prevalence

of frailty may have been either underestimated (the study population had to be sufficiently healthy to be observed over a long period of time) or overestimated (for example, the chosen item for the low physical activity level component might detect some individuals who exhibit limitations in this activity for reasons other than frailty). Finally, our study population was composed of men only, so no inference can be drawn concerning an association between HIV infection and earlier occurrence of frailty in women.

To the extent that frailty in HIV-infected people resembles frailty in HIV-uninfected older adults, studies of frailty in the setting of HIV infection may help to clarify the pathogenesis and early stages of frailty. Additional studies are also needed to define further the correlations between immune markers and functions and FRP, and the impact of HAART on frailty.

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

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