A Frailty-Related Phenotype Before HAART Initiation as an Independent Risk Factor for AIDS or Death After HAART Among HIV-Infected Men

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Background. In the general population, frailty, a late stage of the aging process, predicts mortality. We investigated whether manifesting a previously defined frailty-related phenotype (FRP) before initiating highly active antiretroviral therapy (HAART) affects the likelihood of developing clinical AIDS or mortality after HAART initiation.

Methods. Among 596 HIV-infected men in the Multicenter AIDS Cohort Study whose date of HAART initiation was known within ±6 months and who had an assessable FRP status within 3 years before HAART, survival analyses were performed to assess the effect of FRP manifestation on clinical AIDS or death after HAART.

Results. In men free of AIDS before HAART, AIDS or death after HAART occurred in 13/36 (36%) men who exhibited the FRP before HAART but only in 69/436 (16%) men who did not (hazard ratio = 2.6; 95% confidence interval = 1.4–4.6; $p < .01$). After adjusting for age, ethnicity, education, nadir CD4+ T-cell count, peak HIV viral load, and hemoglobin in the 3 years before HAART, having the FRP at >25% of visits in the 3 years before HAART significantly predicted AIDS or death (adjusted hazard ratio = 3.8; 95% confidence interval = 1.9–7.9; $p < .01$). Results were unchanged when the analysis was restricted to the 335 AIDS-free men who were HAART responders, to the 124 men who had AIDS at HAART initiation, or to the subsets of men for whom indices of liver and kidney function could be taken into account.

Conclusion. Having a persistent frailty-like phenotype before HAART initiation predicted a worse prognosis after HAART, independent of known risk factors.

Key Words: HIV—Aging—Frailty—HAART response—Survival analysis.

IN HIV-uninfected populations, aging is associated with increased risk of specific diseases and with frailty (1–3), a syndrome (4–6) that involves enhanced vulnerability to stressors (6–8). Recent work on frailty suggests that this syndrome is one manifestation of an overall dysregulation (9,10) of multiple interconnected physiologic systems, including immune, neurologic, inflammatory, and endocrine (11,12), in which a multiplicity of defects results in a greater dysfunction than the sum of the individual defects (13–15). Clinically, frailty is characterized by a loss of muscle mass and a decrease in energy and reserves, resulting in declines in strength, exercise tolerance, performance speed, physical activity, and weight (5,6,8). The presence of frailty predicts poor outcomes, including falls, disabilities, loss of independence, and mortality (4,5,16–20).

We recently reported that in the Multicenter AIDS Cohort Study (MACS), a phenotype designed to approximate frailty appeared about 10 years earlier in HIV-infected men who have sex with men (MSM) than in HIV-uninfected MSM (21). The prevalence of this frailty-related phenotype (FRP) increased with increasing duration of HIV infection (21) and decreasing CD4+ T-cell count, both before and during the era of highly active antiretroviral therapy (HAART) (22). These findings support an association between

immunologic compromise and development of frailty and suggest that HIV infection itself may initiate an aging-related physiologic process known to predict mortality.

The importance of frailty in people with HIV infection is not known. We hypothesized that the presence of frailty before starting HAART could independently and adversely affect the response to HAART, including a higher risk of AIDS or death after HAART initiation. Such an effect could result from the multisystem dysregulation and diminution of reserves associated with frailty itself (23,24) or from characteristics associated with HIV infection that induce frailty. To begin to address these hypotheses, the present study investigated the hypothesis that frailty prior to initiation of HAART is a risk factor for subsequent AIDS or death. We studied both men who were AIDS free and men who had AIDS at HAART initiation using data acquired in the MACS.

METHODS

Study Population and Data Acquisition

The MACS is an ongoing prospective study designed to assess the natural and treated histories of HIV infection. The cohort enrolled 4,954 HIV-negative and -positive men who have sex with men in 1984–1985, 668 in 1987–1991, and 1,350 in 2001–2003 at sites located in Baltimore, Chicago, Los Angeles, and Pittsburgh. Detailed descriptions of the MACS have been published (25,26). All participants provided informed consent, and the study was approved by institutional review boards at each site. Study design and questionnaires are available at http://www.statepi.jhsph.edu/macs/macs.html.

Participants returned every 6 months for study evaluations that included a standardized interview, physical examinations, questionnaires (including Short Form-36 (27) and items of the Center for Epidemiological Studies-Depression scale (28)), and collection of blood for laboratory testing and storage in local and national repositories (29). Data on self-identified race and ethnicity were determined through questionnaires. Standardized protocols were used to measure T-lymphocytes (30), with absolute cell counts calculated using a complete blood count (including hemoglobin and platelets) with automated 10,000-cell differential performed on ethylenediaminetetraacetic acid–anticoagulated blood. Plasma HIV RNA (viral load) was assessed using either the Roche standard assay (sensitive to 400 copies/mL; Roche Diagnostics, Nutley, NJ) or the Roche ultrasensitive assay (sensitive to 50 copies/mL). HIV seropositivity was determined by a positive enzyme-linked immunosorbent assay confirmed by Western blot.

Serum liver enzymes (AST and ALT) and creatinine (Scr) were not measured prospectively, but pre-HAART values were available on a subset of men who had been randomly selected for retrospective testing because they had initiated HAART. Biomarkers of liver function were scores on the fibrosis (FIB-4) (31) and AST to platelet ratio (APRI) (32) scales and were calculated as follows:

$$FIB\text{-}4 = (\text{age [yr]} \times \text{AST [U/L]}) / ((\text{Platelet count } [10^9/\text{L}]) \times (\text{ALT [U/L]})^{1/2}),$$

$$APRI = (\text{AST} / \text{ULN}) / \text{Platelet count } [10^9/\text{L}] \times 100,$$

where 50 U/L was used as the upper limit of normal (ULN).

These biomarkers were available on 437 of the 596 men in the study population (73%). Biomarkers of kidney function were Scr or estimated glomerular filtration rate (eGFR (33)) calculated as follows:

$$eGFR = 186 \times Scr^{-1.154} \times age^{-0.203} \times (1.212 \text{ if black})$$
$$(\text{Modification of Diet in Renal Disease [MDRD] equation}).$$

These biomarkers were available on 229 of the 596 men in the study population (38%).

HAART was defined using self-reported data on medication use according to the U.S. Department of Health and Human Services Kaiser Panel guidelines (34) as (a) two or more nucleoside reverse transcriptase inhibitors (NRTIs) in combination with at least one protease inhibitor or one non-nucleoside reverse transcriptase inhibitor (NNRTI), (b) one NRTI in combination with at least one protease inhibitor and at least one NNRTI, (c) a regimen containing ritonavir and saquinavir in combination with one NRTI and no NNRTIs, and (d) an abacavir- or tenofovir-containing regimen of three or more NRTIs in the absence of protease inhibitors and NNRTIs. Combinations of zidovudine (AZT) and stavudine (d4T) with a protease inhibitor or an NNRTI were not considered HAART. Medical records were used to confirm AIDS diagnoses, and death certificates were used to document deaths.

The present analysis was based on a FRP recently defined among the HIV-negative men enrolled in the MACS (21). This definition used data gathered by standardized questionnaires at MACS study visits after April 1994 to match as closely as possible the clinical phenotype of frailty. As proposed and validated as a medical syndrome (4,5), the frailty phenotype is defined by the presence of three or more of five components (weight loss, exhaustion, weakness, slowness, and low physical activity). Of these components, all except weakness could be assessed with MACS questionnaire data as previously described (21). Therefore, the FRP was identified by the presence of at least three of the remaining four components. Prevalence of the FRP among HIV-negative MACS participants was 1% for those aged <55 years and 4.4% for those aged 65 years and older (21).

The present study included all HIV-seropositive men who (a) initiated HAART before 2001, (b) had an evaluable FRP status for one or more study visits in the 3 years before HAART initiation, and (c) had a date of HAART initiation that was known to within ±6 months. Date of HAART initiation was defined as the midpoint between the dates of the

last visit without use of HAART and the first visit with use of HAART.

Statistical Analysis

Univariate comparisons of characteristics among groups were assessed using chi-square and Wilcoxon tests for categorical and continuously distributed variables, respectively.

For survival analyses by Kaplan–Meier curves (and logrank test) and Cox proportional hazards models, the study outcome was the onset of a clinical AIDS diagnosis (35) or death for those who were AIDS free at HAART initiation and death for those with AIDS before HAART initiation. Analyses were conducted separately for those who had never had AIDS before HAART initiation and those who had. AIDS was defined clinically using the CDCP 1993 criteria (35) except that a CD4+ T-cell count of <200 cells/uL was not considered AIDS. Time to event was the time from date of HAART initiation to either the outcome or the censoring. Data were analyzed by intention-to-continue treatment, ignoring treatment changes, and interruptions. The main exposure was the manifestation of the FRP within the 3 years before HAART initiation. This exposure was analyzed in three ways: (a) FRP present at any visit in the 3 years before HAART (ever vs never), (ii) FRP present at >25% versus ≤25% of the visits within this period (the denominator being the number of visits at which FRP status was evaluable), and (iii) FRP present at ≥2 visits within this period among men with at least two visits at which FRP was evaluable. The rationale for the latter definitions was that they addressed the effect of the "burden" of frailty, which is different from simply the presence or absence of the FRP at a single assessment. Cox models were adjusted for age at HAART initiation, education (college or higher vs lower), ethnicity (White non-Hispanic vs other), and the following variables during the 3 years before starting HAART: nadir CD4+ T-cell count, maximum viral load ($\log_{10}$-transformed), and nadir hemoglobin (in grams per deciliter). To account for liver disease as a potential confounder, we used an additional multivariate Cox model, adjusting for last available value for FIB-4 prior to HAART in addition to the variables listed earlier. (Adjustment for APRI instead of FIB-4 led to similar results, which are not given.) Multivariate models that added serum creatinine or eGFR to the liver disease model were also performed to take kidney disease into account; these analyses were limited by the fact that these data were available for only a subset of the cohort (see "Results").

In addition to stratifying by history of AIDS at HAART initiation, we also conducted separate analyses restricted to HAART responders, that is, men who achieved viral suppression (defined as a viral load <1,000 copies/mL) within 1 year following HAART initiation. The hypothesis that associations between each quantitative variable (CD4+ T-cell count, $\log_{10}$(viral load), age, hemoglobin, FIB-4, and eGFR)

and time to AIDS or death were log linear in Cox models was checked using restricted cubic spline functions (36,37) with knots located at the 5th, 50th, and 95th percentiles of the distribution of each quantitative variable. The hypothesis was acceptable (ie, p value for nonlinear association >.10) for all variables, except for eGFR among men AIDS free at HAART initiation and FIB-4 among men with AIDS at HAART initiation. The proportional hazard assumptions for the binary variables "ever FRP" and "FRP at >25% of visits" were met for all models. The cutoff date for the analysis was April 30, 2005. SAS V9.1 (SAS Institute, Cary, NC) was used for statistical analyses.

RESULTS

Study Population and Follow-up

789 HIV-positive men enrolled before 2001 initiated HAART. Entry criteria for the present analysis were met by 596 (76%) of whom 472 were AIDS free at HAART initiation and 124 had had AIDS by this time. The median follow-up after HAART initiation until an outcome (AIDS or death for the group without AIDS at HAART initiation and death for the group with AIDS at HAART initiation) or censoring was 7.1 years (interquartile range = 4.4–8.2), providing a total follow-up of 3,619 person-years. Table 1 summarizes baseline characteristics of men with and without the FRP before HAART initiation. The median number of visits at which the FRP status was assessable within the 3 years before starting HAART was 4 (of a maximum of 6). Men with the FRP within the 3 years prior to HAART initiation were similar to those without the FRP by year of HAART initiation, age, virological response to HAART, duration of HIV infection, and demographics.

Import of the FRP Among Men Who Were AIDS Free at HAART Initiation (n = 472)

Men with the FRP ($n = 36$, 8%) had slightly higher maximum viral loads ($p = .01$) and slightly lower nadir hemoglobin ($p < .01$) and nadir CD4+ cell counts ($p = .09$) pre-HAART than those without the FRP ($n = 436$, 92%; Table 1). As shown in Table 2, men with the FRP were more likely to develop AIDS or death than those without the FRP prior to HAART. The incident AIDS-defining illnesses were similar in the two groups (data not shown). U.S. guidelines for starting HAART (38) were met within the 3 years before HAART by 29 of the 36 men with the FRP (81%) compared with 74% (322/436) of the men without the FRP ($p = .38$).

In univariate analyses, all three ways of analyzing expression of the FRP showed a significant association with time to AIDS or death. First, men who manifested the FRP at least once in the 3 years before HAART initiation were significantly more likely than those without this phenotype to develop AIDS or to die after starting HAART (Figure 1a; $p_{\text{logrank}} < .01$). The corresponding unadjusted hazard ratio

Table 1. Characteristics of the Study Population at HAART Initiation According to AIDS and FRP Status

	No AIDS Before HAART (N = 472)		AIDS Before HAART (N = 124)		
	No FRP* (N = 436)	FRP* (N = 36)	No FRP* (N = 77)	FRP* (N = 47)	Total (N = 596)
Date of HAART initiation[†]	2/97 (7/96–1/98)	10/96 (5/96–7/97)	6/96 (2/96–1/97)	7/96 (2/96–3/97)	12/96 (5/96–11/97)
Education higher than or equal to college, n (%)	241 (56)	16 (46)	51 (66)	29 (62)	337 (57)
Ethnicity = White non-Hispanic, n (%)	365 (84)	31 (86)	66 (86)	41 (87)	503 (84)
Age[†]	43 (38–48)	44 (40–49)	43 (39–46)	43 (39–46)	43 (38–48)
Maximum viral load (log$_{10}$ copies/mL)*,[†]	4.8 (4.3–5.2)	5.2 (4.6–5.4)[‡]	5.3 (4.8–5.6)	5.3 (5.0–5.7)	5.0 (4.4–5.3)
Nadir CD4+ cell count (per mm³)*,[†]	271 (163–388)	239 (86–393)	116 (26–239)	61 (15–170)[‡]	226 (125–359)
Nadir Hgb before HAART (g/dL)*,[†]	13.8 (13.1–14.5)	13.2 (11.2–14.2)[‡]	12.7 (11.8–13.7)	11.4 (10.0–13.1)[‡]	13.6 (12.5–14.3)
Duration of HIV infection (y)[†,§]	11.6 (8.5–12.6)	11.5 (8.6–12.0)	11.5 (10.3–12.2)	11.6 (10.6–12.1)	11.6 (8.7–12.5)
Among seroconverting men	7.7 (5.4–11.4)	8.5 (5.6–11.5)	9.0 (7.1–10.9)	9.0 (6.7–10.8)	8.3 (5.6–11.3)
Among seroprevalent men	11.9 (11.0–12.8)	11.8 (11.1–12.4)	11.7 (11.3–12.4)	11.8 (11.4–12.5)	11.8 (11.2–12.7)
HAART responders, n (%)[∥]	311 (77)	24 (71)	38 (58)	24 (59)	397 (73)
Number of visits assessable for FRP*,[†]	5 (4–6)	4 (4–6)	4 (3–5)	4 (3–5)	4 (4–6)
>25% manifesting FRP visits, n (%)*	0	18 (50)	0	28 (60)	46 (8)

Notes: FRP = frailty-related phenotype; HAART = highly active antiretroviral therapy; Hgb, hemoglobin.

*Within the 3 years before HAART.

[†]Median (interquartile range).

[‡]$p \leq \cdot 05$ when comparing men with FRP with those without FRP at HAART initiation FRP.

[§]Durations calculated from estimated date of seroconversion for seroconverting men (N = 178) and from first HIV-positive visit for seroprevalent men (N = 418).

[∥]Defined as a viral load of <1,000 copies/mL within 1 year after starting HAART, % are based on nonmissing data.

(HR) from a Cox model was 2.6 (95% confidence interval [CI] = 1.4–4.6; $p < .01$). Second, the corresponding figures for having the FRP at >25% of study visits in the 3 years before HAART (n = 18), as opposed to ≤25% (n = 454), were $p_{logrank} < .01$ (Figure 1b) and unadjusted HR of 4.7 (95% CI = 2.4–9.1; $p < .01$). Finally, having the FRP at ≥2 visits in this period (n = 9) led to an HR of 3.7 (95% CI = 1.5–9.0; $p = .01$). In this last analysis, outcomes of AIDS or death occurred in 5 of 9 (56%) men who had the FRP at ≥2 visits as opposed to 68 of 422 (16%) who had the FRP at zero or one visit. This difference was not due to fewer visits in the latter group because this group had a higher median number of visits where the FRP was assessable than the group with the FRP at ≥2 visits (median [interquartile range] = 5 (4–6) vs 4 (4,5), respectively).

In multivariate analyses that adjusted for ethnicity, education, age, nadir CD4+ T-cell count, nadir hemoglobin, and maximum viral load pre-HAART, only the second (>25% of visits with the FRP vs ≤25%) and third (≥2 visits with the FRP vs <2) analyses remained significant. Specifically, the association of FRP status at HAART initiation (ever vs never) with AIDS or death after HAART was attenuated to an adjusted HR (aHR) of 1.5 (95% CI = 0.8–2.9; $p = .25$). However, the aHR for having the FRP at >25% of visits before HAART was 3.8 (95% CI = 1.9–7.9 relative to ≤25% of visits; $p < .01$; Table 3). In this analysis, older age at HAART initiation and higher viral load peak were also independently and significantly associated with subsequent AIDS or death (Table 3). Including hepatitis C virus (HCV) status at HAART initiation in this model did not affect the association between FRP and AIDS or death (aHR = 4.3; $p < .01$) nor was this association affected by excluding wasting syndrome diagnoses from the definition of AIDS by taking into account hemoglobin as a binary variable according to values <12 versus ≥12 g/dL or by further adjusting for the year of HAART initiation, smoking habits within the 3 years before HAART, or the number of visits at which the FRP was assessable (data not shown). Finally, having the FRP at ≥2 visits showed an aHR = 4.0 (95% CI = 1.5–10.4; $p < .01$). This latter result should be interpreted with caution because it was based on only nine men with ≥2 visits with the FRP in the 3 years before HAART. The results hereafter will therefore refer to the second multivariate analysis only.

To further understand the meaning of having the FRP, the second multivariate analysis was performed for each of the four components of the FRP individually. Having a component at >25% of the visits (vs ≤25%) was positively associated with time to AIDS or death as follows: exhaustion (aHR = 2.7; $p < .01$), slowness (aHR = 2.6; $p = .04$), physical activity (aHR = 1.8; $p = .02$), and weight loss (aHR = 1.7; $p = .10$). Thus, the individual FRP components were not as strongly associated with outcomes as the FRP itself (aHR = 3.8).

Table 2. Outcomes Among 472 MACS Participants Who Were AIDS Free at HAART Initiation According to FRP Status Before HAART

	FRP Before HAART*		Total
Outcome	No (n = 436)	Yes (n = 36)	(n = 472)
No outcome (%)	367 (84)	23 (64)	390 (83)
AIDS or death (%)	69 (16)	13 (36)	82 (17)
Among AIDS or death			
AIDS (%)	44 (10)	8 (22)	52 (11)
Death with no previous AIDS (%)	25 (6)	5 (14)	30 (6)

Notes: FRP = frailty-related phenotype; HAART = highly active antiretroviral therapy.
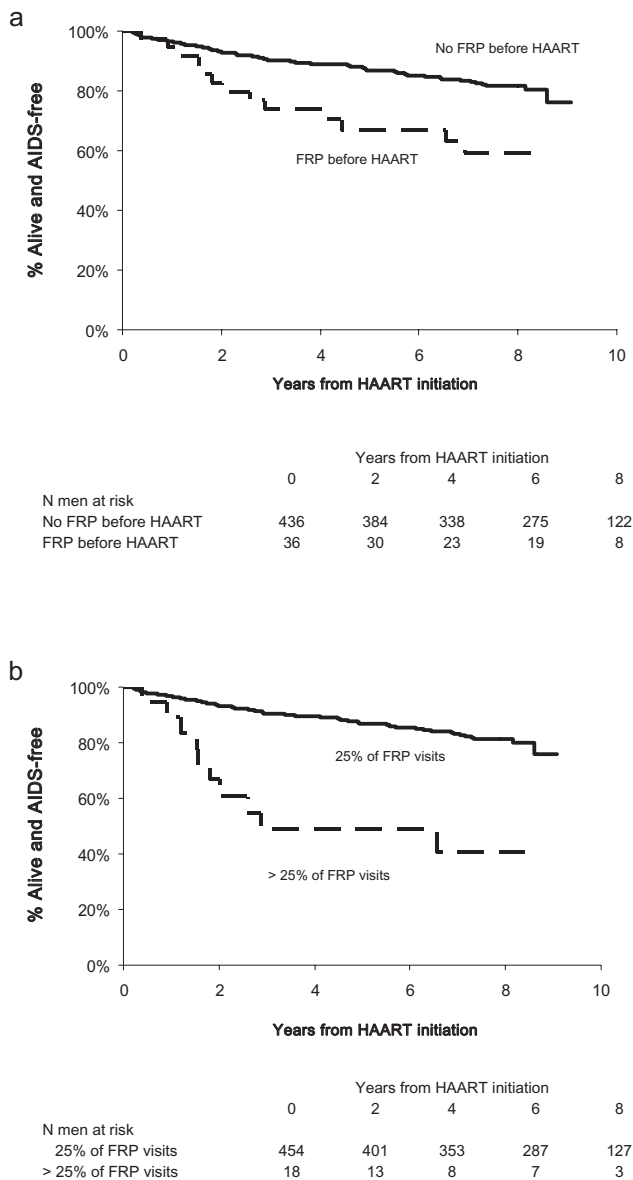
*FRP within the 3 years before HAART

a

	Years from HAART initiation				
	0	2	4	6	8
N men at risk					
No FRP before HAART	436	384	338	275	122
FRP before HAART	36	30	23	19	8

b

	Years from HAART initiation				
	0	2	4	6	8
N men at risk					
25% of FRP visits	454	401	353	287	127
> 25% of FRP visits	18	13	8	7	3

Figure 1. Kaplan–Meier estimates of progression to AIDS-defining illness or death after highly active antiretroviral therapy (HAART) initiation among 472 men in the Multicenter AIDS Cohort Study who were AIDS-free at HAART initiation, stratified by (**a**) presence or absence of the frailty-related phenotype (FRP) in the 3 years before HAART or (**b**) according to the percentage of FRP visits in the 3 years before HAART (>25% vs ≤25%).

It was possible that the association of the FRP with AIDS or death was confounded by other diseases. To take into account liver disease besides anemia (as was described earlier by adjusting for nadir hemoglobin), we performed the adjusted analysis for the 365 (77%) men for whom the FIB-4 biomarker was available. The inferences described earlier were not affected. Specifically, manifesting the FRP at least once in the 3 years before HAART was not independently associated with AIDS or death (aHR = 1.3; p = .64 when FIB-4 was not included in the model and aHR = 1.3; p = .56 when it was), but having the FRP at >25% of the visits in the

3 years before HAART was (aHR = 5.5; p < .01 when FIB-4 was not included in the model and aHR = 5.6; p < .01 when it was). A separate adjustment for eGFR in men with serum creatinine data (n = 231, 49%) led to similar results (data not shown). These results are limited by their smaller sample sizes, but it should be noted that they are based on random samples of the cohort who initiated HAART and are thus unbiased regarding the outcomes studied.

Finally, we examined whether the association of FRP with AIDS or death could be explained by differences in viral suppression after HAART. This analysis was restricted to the 335 men who suppressed their viral load to <1,000 copies/mL within 1 year after starting HAART. This included 67% (24/36) of men who had the FRP before HAART and 71% (311/436) of those who did not (p = .55). In these men, both having the FRP at one or more pre-HAART visits and having the FRP at >25% of pre-HAART visits were significantly associated with AIDS or death after HAART (aHR = 3.0; 95% CI = 1.3–7.2; p = .01 and aHR = 9.1; 95% CI = 3.6–23.3; p < .01, respectively). These data suggest that the association of the FRP with the outcomes studied was not due to an association of the FRP with degree of viral suppression after HAART.

Import of the FRP Among Men Who Had AIDS at HAART Initiation (n = 124)

Among these men, the proportion who had the FRP at least once within the 3 years before HAART was higher than in the AIDS-free men (n = 47, 38% vs n = 36, 8%). Again, men who had the FRP had significantly lower nadir CD4+ counts than those who did not, but other disease parameters including viral load were similar for both groups (Table 1). After HAART, 19 (40%) of the 47 men who had the FRP before HAART died compared with only 15 (19%) of the 77 who did not. This difference was significant in univariate analysis (Figure 2a; $p_{logrank}$ = .01), with an unadjusted HR of 2.3 (95% CI = 1.2–4.6; p = .02). Similarly, manifesting the FRP in >25% of visits in the 3 years before HAART (n = 28) was significantly associated with death, relative to not manifesting it (n = 96; Figure 2b; $p_{logrank}$ = .01), with an unadjusted HR of 2.6 (95% CI = 1.3–5.1; p = .01).

The significance of having the FRP at least once within the 3 years before HAART (aHR = 2.2; 95% CI = 1.1–4.6; p = .04) or at >25% of visits (aHR = 2.4; p = .03; Table 3) persisted after adjustment for the covariates cited earlier but not after an additional adjustment for HCV status prior to HAART (aHR = 1.8; 95% CI = 0.8–4.2; p = .16). In this population, having ≥2 visits with the FRP (20/124) was again associated with death, both before adjustment (HR = 2.9; 95% CI = 1.4–6.2; p < .01) and after (aHR = 2.4; 95% CI = 1.0–5.8; p = .05), whereas men with ≥2 and <2 visits with the FRP had the same median number (n = 4) of visits where the FRP was assessable. Finally, among the 62 men in this group who achieved viral suppression after HAART,

Table 3. Impact of Presence of a FRP and Other Factors Within the 3 Years Before HAART Initiation on Subsequent Occurrence of Clinical AIDS or Death Among 596 Men Enrolled in the MACS Using Multivariate Cox Models

Exposures at HAART Initiation	AIDS Free at HAART (N = 472)		AIDS at HAART (N = 124)	
	aHR* (95% CI)	p Value	aHR† (95% CI)	p Value
Education higher than or equal to college	1.10 (0.68–1.76)	.70	0.92 (0.45–1.89)	.82
Ethnicity = White non-Hispanic (vs others)	1.36 (0.67–2.79)	.40	0.75 (0.28–2.01)	.56
Age (per 10-year increase)	1.42 (1.02–1.99)	.04	1.28 (0.76–2.15)	.36
Nadir CD4+ T-cell count (per 100 cell/mm^3 increase)‡	0.88 (0.74–1.04)	.13	0.94 (0.70–1.26)	.66
Maximum plasma viral load (per 1 log$_{10}$ copies/mL increase)‡	1.94 (1.26–3.00)	<.01	1.19 (0.65–2.20)	.57
Nadir Hgb before HAART (per 1 g/dL increase)‡	0.86 (0.73–1.01)	.07	0.99 (0.82–1.21)	.95
Proportion of FRP visits before HAART >25% (vs ≤25%)‡	3.83 (1.86–7.92)	<.01	2.44 (1.11–5.37)	.03

Notes: aHR = HRs adjusted for variables listed in the table; CI = confidence interval; FRP = frailty-related phenotype; HAART = highly active antiretroviral therapy; Hgb = hemoglobin; HR = hazard ratio.
  *Adjusted HRs for AIDS/death.
  †Adjusted HRs for death only.
  ‡Within the 3 years before HAART.

the proportion of pre-HAART visits with the FRP (>25% vs ≤25%) was again significantly associated with death (HR = 4.8; 95% CI,= 1.3–18.0; *p* = .02). This was also true among the 72 men who had data on liver function, both when FIB-4 was not included in the model (aHR = 6.3; *p* = .02) and when it was (aHR = 5.9; *p* = .04).

DISCUSSION

The results of this study indicate that the presence of a FRP in HIV-positive men prior to HAART initiation was an independent predictor of development of AIDS or of death despite HAART in most, but not all, of the analyses conducted. This was true among both men who did not have AIDS and among those who did. Among the subset of men who achieved virologic suppression within 1 year after HAART initiation, it was true in all analyses. Furthermore, the association of the FRP with outcomes was independent of pre-HAART levels and nadir of hemoglobin and CD4+ T-cell count, peak HIV viral load, and other potential confounders, including liver and kidney function in the men who had these data available (78% and 49%, respectively, among the AIDS-free men at HAART initiation). In addition, HCV status had no effect on these findings in AIDS-free men and only a minor effect in the men with AIDS. Thus, the association between the FRP and time to AIDS or death did not seem to be confounded by many of the HIV-related and -unrelated biomarkers that are associated with mortality after initiation of antiretroviral therapy (39–41). The FRP as defined in this study uses extant data from the MACS cohort and has been demonstrated to relate to a previously validated medical syndrome of frailty (21).

In the population of men who were AIDS free at HAART initiation, the adjusted association between the FRP and time to AIDS or death was significant when using proportion of visits with FRP (>25% vs ≤25%) or when using two or more visits with the FRP as the cutoff but not when using

FRP ever versus never. A stronger association between the FRP and time to AIDS or death was also observed among the subpopulation of men AIDS free at HAART who achieved virologic suppression within 1 year after HAART when the FRP was used as >25% versus ≤25% of the visits than when using FRP ever versus never. This finding suggests the hypothesis that a certain "burden" or threshold of frailty is required to affect later outcomes as has been hypothesized (42–44). The clinical implication of this would be that a recurrent or sustained presentation of the FRP may indicate an increased risk for AIDS or death after HAART. Although monitoring the proportion of visits with the FRP may be difficult in clinical settings, our data also suggest that the number of visits with the FRP predicted outcomes approximately as well as the proportion of visits. This may provide a more clinically feasible method of monitoring expression of the FRP and of testing its clinical import. However, this suggestion should be considered with caution because it is based on relatively few observations.

If confirmed in additional studies, the finding that the FRP independently predicts poorer outcomes after initiation of HAART has a number of important implications. First, biologically, it supports prior findings that frailty, a syndrome associated with aging and with catabolic diseases including congestive heart failure, may be a final common pathway that is initiated by these diseases but then independently modifies the outcomes associated with the precipitating pathology. Second, and clinically, it helps to explain differences in clinical outcomes among those who receive HAART, and it may—in the short-term—identify ways to distinguish those at low or high risk of poor outcomes after HAART. This may also suggest a need for additional therapeutic approaches for HIV-positive people with the FRP as recently proposed for older adults at risk of poor surgical outcomes after elective surgery in whom a preoperative screen for frailty was the best tool for identifying the high-risk group (45). A related point is that because the FRP is associated with low CD4 T-cell counts, FRP assessment in
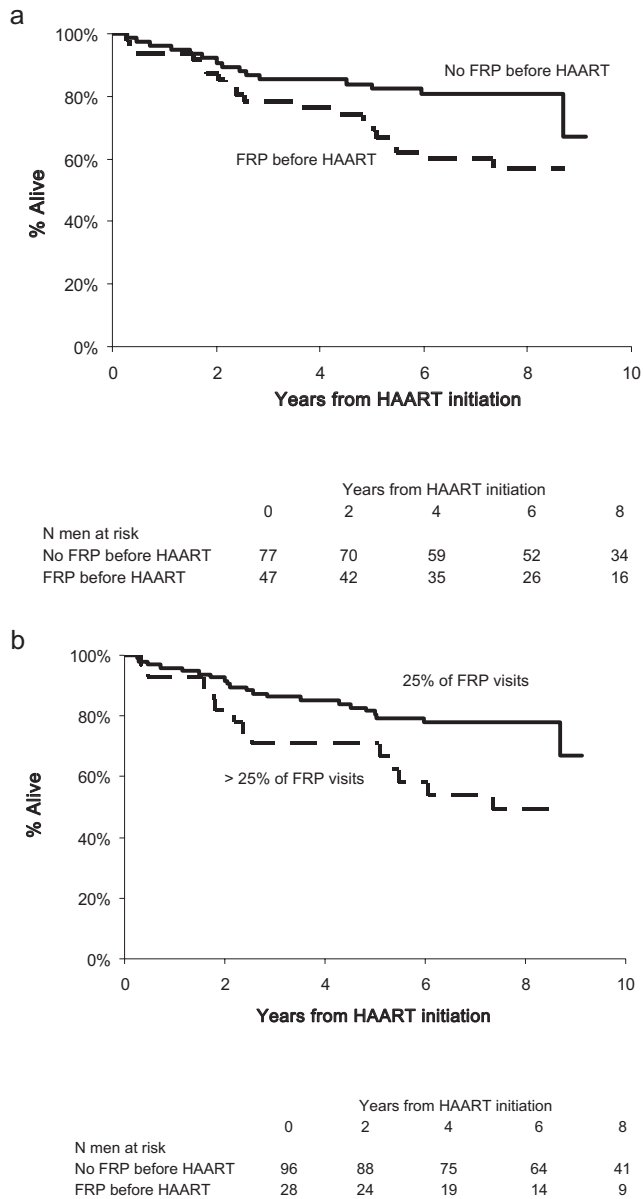
	Years from HAART initiation				
	0	2	4	6	8
N men at risk					
No FRP before HAART	77	70	59	52	34
FRP before HAART	47	42	35	26	16

	Years from HAART initiation				
	0	2	4	6	8
N men at risk					
No FRP before HAART	96	88	75	64	41
FRP before HAART	28	24	19	14	9

Figure 2. Kaplan–Meier limit estimates of progression to death after highly active antiretroviral therapy (HAART) initiation among 124 men in the Multicenter AIDS Cohort Study who had AIDS before HAART initiation, stratified by (**a**) presence or absence of the frailty-related phenotype (FRP) in the 3 years before HAART or (**b**) according to the percentage of FRP visits in the 3 years before HAART (>25% vs ≤25%).

settings where CD4 T-cell testing is limited could help identify people who should be receiving HAART, although the reversibility of the FRP by HAART remains to be studied.

These biological and clinical implications may be related. Although the effect sizes were relatively imprecise, our finding that the FRP as a whole was more predictive of AIDS or death than any of its four components taken individually is consistent with prior reports validating the frailty phenotype as a distinct clinical syndrome (4,5). Furthermore, as with diabetes mellitus, where the duration of the

illness predicts mortality (46), our finding that HIV-positive men who had the FRP at more than 25% of visits were at significantly elevated risk of poor outcomes suggests that it is the persistence of the phenotype over time that provides greatest specificity of the relationship with adverse outcomes. This would be consistent with other reports indicating that severity of frailty is associated with adverse outcomes, such as loss of independence (20) and mortality (5). Other prior work indicates that the severity of frailty is related to the number of physiologic systems that are dysregulated (10), with the characteristics of a complex system (15). Ultimately, we may be seeing evidence of physiological dysregulation that can be initiated by HIV infection, other catabolic diseases, or physiologic processes of aging itself, which results in an independent process of fraying of the complex system of a resilient organism and in an emergent property of greater vulnerability (8). The extent to which specific underlying conditions contribute to this fraying was not evaluable in this study, but the specific conditions examined (ie, anemia and liver and renal disease) did not materially affect the relationship between the FRP and the risk of AIDS or death after starting HAART. However, the analysis of contributions of underlying conditions was necessarily incomplete and was also limited by missing data for liver and particularly renal status.

Other limitations of the study should be mentioned. The data were obtained from an observational study, so it cannot be concluded that frailty was a causal factor of AIDS or death. As mentioned, even after the adjustments made, residual confounding may still have been present due to unmeasured confounders. Because we measured a frailty-related phenotype rather than the clinically validated frailty phenotype (5), we may have misclassified some men as being frail (or nonfrail); although such nondifferential misclassification would be expected to bias estimates conservatively, the present results should still be confirmed with the validated frailty phenotype. In this study, the majority of men initiated HAART before 1998, and most had been exposed to mono- and dual-therapy prior to HAART; therefore, the present study is not representative of people who start HAART now. Furthermore, HAART regimens have become less toxic since 1998, which theoretically could affect relative survival, although adjustment for the time of HAART initiation did not change the results in this study. Our study population was exclusively male and predominantly White, so our results cannot be generalized to men of other ethnicities or to women. Although significant associations were observed, the number of men who had the FRP was small (less than 10% of men who were AIDS free at HAART initiation). Because of the small number of men who had both AIDS and FRP before HAART initiation, we cannot exclude an effect of particular AIDS-defining conditions on the outcome of mortality. Despite these limitations, however, the present findings support the need for further studies of prevalence and mechanisms of frailty in people with HIV infection.

The findings of this study suggest that HIV-infected individuals may respond better to antiretroviral treatment if started as early as possible in the course of frailty. This possibility may be less important when HAART is initiated at higher CD4+ cell counts at which frailty is less common (22). However, it could be more important in places where CD4+ T-cell counts and viral loads, and HAART itself, are not readily available. The five criteria for frailty can be assessed relatively easily and inexpensively through questionnaires and performance tests, and the four components of the FRP can be assessed simply through questionnaires. Interventions to identify HIV-infected persons at high risk of frailty and to prevent or reverse onset of frailty regardless of HIV status are needed everywhere.

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