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Research Article

Long-term Trajectories of C-Reactive Protein Among Men Living With and Without HIV Infection in the Multicenter AIDS Cohort Study

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Abstract

Background: C-reactive protein (CRP) is an inflammatory biomarker associated with all-cause mortality and morbidities such as cardiovascular disease. CRP is increased with HIV infection and thought to increase with age, though trajectories of CRP with aging have not been well characterized. We investigated trajectories of CRP in men from the Multicenter AIDS Cohort Study, according to HIV infection and HIV viral load status.

Methods: CRP measurements from 12 250 serum samples, provided by 2132 men over a span of 30 years, were categorized by HIV status at sample collection: HIV uninfected (HIV–, n = 1717), HIV infected with undetectable RNA (HIV+ suppressed, n = 4075), and detectable HIV RNA (HIV+ detectable, n = 6458). Age-related trajectories of CRP were fit to multivariable linear mixed models; we tested for differences in trajectories by HIV status.

Results: CRP increased with age in all sample groups. HIV+ detectable and HIV+ suppressed samples had higher CRP than HIV– samples throughout the observed age range of 20–70 years ($p < .05$). CRP concentrations at age 45 years were 38% (95% CI: 26%–50%) and 26% (15%–38%) higher in HIV+ detectable and HIV+ suppressed samples, respectively, relative to HIV– samples. HIV+ detectable samples showed more rapid linear increases with age (8% higher/decade, 0.3%–16%) than HIV– samples.

Conclusions: We observed higher concentrations of CRP across 5 decades of age in men living with HIV, and steeper increases with age in men with detectable HIV RNA, relative to HIV– men. These results are consistent with a contribution of inflammation to the higher risk of age-related comorbidities with HIV infection.

Keywords: Aging, Biomarkers, CRP, Inflammation, Longitudinal

People living with HIV (PLWH) face a higher risk than HIV-uninfected (HIV–) people for aging-associated conditions, leading some to postulate an accelerated aging process (1–3), although this has been disputed (4). Effectively treated HIV infection is characterized by chronic low-level inflammation, with persistent elevations of some markers of inflammation and immune activation despite suppression of HIV replication (5). Inflammation, in turn, has been associated with a higher risk of mortality and with aging-related morbidities among both PLWH and HIV– people. C-reactive protein (CRP) is a marker of general inflammation that is commonly measured in clinical practice and has been linked with disease outcomes in PLWH. For instance, in the Multicenter AIDS Cohort Study (MACS), concentrations of CRP among virologically suppressed PLWH predicted all-cause mortality (6) and were associated with HIV disease progression (7).

CRP is an acute-phase protein synthesized in the liver in response to proinflammatory cytokines, particularly interleukin 6. CRP binds to phosphocholine on necrotic and apoptotic cells, triggering the

complement system (8). Its concentration in plasma is highly sensitive to inflammatory conditions, such as infections, and can increase from a normal concentration of less than 3 mg/L to over 100 mg/L and even 500 mg/L within days (9). Such large increases are generally transient, but concentrations can persist at high levels for longer periods of time in the face of some chronic infections, such as HIV, and inflammatory diseases, such as Crohn's disease (7,10).

In contrast, mildly elevated CRP concentrations (3–10 mg/L) can persist for many years without overt disease in both PLWH and HIV– people and may reflect ongoing subclinical inflammatory processes (11). Mildly elevated CRP concentrations have been associated with cardiovascular disease (12–17), obesity (11), diabetes mellitus (16), frailty (18,19), and all-cause mortality (20), though Mendelian randomization studies suggest that at least some of these observed associations are not causal (15,20,21). Measurements of CRP exceeding 10 mg/L are usually thought to represent acute inflammatory events, but concentrations in this range can be associated with chronic disease (22,23).

CRP concentrations are thought to increase with age, supporting the notion that chronic inflammation contributes to the aging process. Much of the evidence for these beliefs, and for CRP-outcome associations, comes from cross-sectional studies (24,25) or from studies with a single measurement of CRP preceding outcomes (26). Although a few studies have obtained serial CRP measurements within individuals over several years (27,28), most have employed 2 measurements per individual (13,14,17,22,29). These studies have not provided a full understanding of the natural history of CRP with age, and there is a paucity of long-term longitudinal data on aging and CRP. Furthermore, it is unknown whether CRP concentrations follow similar age-related trajectories in PLWH as in comparable HIV– individuals. Thus, several critical research questions about the relationship between CRP and aging remain unanswered for both PLWH and HIV-uninfected people.

To address these questions, we analyzed CRP measurements from stored serum samples longitudinally collected from men between 1984 and 2014 in the MACS. We report here on the age-related trajectories of CRP in men living with and without HIV infection and on how HIV suppression by effective combination antiretroviral therapy (cART) may influence these trajectories. We also investigated whether extremely high CRP concentrations are associated with HIV infection, and what factors may predispose to such high values.

Method

Study Population and Sample Selection

The MACS is an ongoing prospective cohort study of HIV infection among men who have sex with men at 4 sites in the United States: Baltimore, MD/Washington, DC; Chicago, IL; Los Angeles, CA; and Pittsburgh, PA (30). Men in the cohort are evaluated at semiannual study visits that include standardized interviews, physical examinations, laboratory analyses, and storage of plasma and serum at −80°C. MACS study protocols at all sites were approved by their local IRBs, and all participants provided informed consent for all procedures.

CRP testing of stored serum from selected person-visits was performed in 2 previous substudies (Supplementary Figure 1). In the first (5), samples from 1984 to 2009 were selected from all MACS participants who (i) had a known date of HIV seroconversion (including 1 sample before seroconversion and samples at 1-year intervals thereafter) and/or (ii) had initiated cART (including samples immediately before and after antiretroviral treatment (ART) initiation and then at 2-year intervals thereafter). These overlapping groups included 10 998 person-visits. Up to 4 samples per person were also selected from 250 persistently HIV– men (n = 950 person-visits). These included all HIV- men with active hepatitis C (HCV) infection, whose inclusion was intended to assess as precisely as possible the effects of HCV infection, which is known to reduce CRP concentrations (31–33). In the second substudy, 1 sample was selected from a visit in 2013–2014 from all men who initiated cART after 2010 and who had undetectable HIV RNA at that visit (n = 182) and from 120 demographically similar HIV– MACS participants.

For the present study, we classified participants' samples into 3 groups based on the participants' status at sample provision: (i) HIV-uninfected ("HIV–"), (ii) HIV+ with undetectable plasma HIV RNA ("HIV+ suppressed"), and (iii) HIV+ with detectable plasma HIV RNA ("HIV+ detectable"). Men could contribute samples at more than 1 visit and to more than one of these 3 groups. For example, someone who entered the MACS as HIV–, became HIV+, and later initiated cART and suppressed HIV replication could contribute data to all 3 study groups. Specific contributions of men to the 3 groups are given in Supplementary Table 1.

CRP and Covariate Measurement/Definitions

CRP concentrations were measured by a reference laboratory (Quest Diagnostics, Madison, NJ) using a high-sensitivity immunonephelometric assay (5). Plasma HIV RNA concentration (HIV viral load) was quantified with the Roche Amplicor assay (Roche Molecular Systems, Branchburg, NJ), sensitive to 50 copies/mL (60% of samples), the Roche COBAS Taqman assay sensitive to 20 copies/mL (4%), and older assays sensitive to 400 (Roche Amplicor 2nd generation, 35%) or 500 copies/mL (Quantiplex HIV RNA 2.0; Chiron Corporation, Emeryville, CA, <1%). Measurements below the sensitivity of the assay used for that sample were classified as undetectable; 96% of such samples were below 50 copies/mL. CD4+ T-lymphocyte counts were measured with flow cytometry.

We chose covariates that might be expected to affect CRP concentrations but not lie in the causal pathway from HIV infection to inflammation (eg, smoking and obesity, but not chronic kidney disease). HCV infection was defined by the presence of HCV RNA in plasma. Race was assessed by self-report at baseline. Current cigarette smoking and injection drug use were assessed by self-report at each MACS study visit and dichotomized as yes/no. Obesity was defined as a body mass index ≥ 30 kg/m^2. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or use of antihypertensive medications. Diabetes mellitus was defined as a hemoglobin A1C level ≥ 6.5%, a fasting glucose level ≥ 126 mg/dL, or use of antidiabetic medications.

Statistical Methods

Because the distribution of CRP concentrations was highly right skewed, CRP concentrations were natural log-transformed for analyses. For the 610 (5%) samples with concentrations below the lower limit of quantification (0.2 mg/L), we interpolated values via a random draw from lognormal distributions fit to CRP measurements, stratified by the 3 HIV study groups.

To examine individual trajectories of CRP concentrations with age, we fit linear mixed-effects models to CRP concentrations, with age as the primary exposure of interest. For these analyses, we excluded samples from men younger than 20 (n = 7) or older than 70 (n = 52) years at sample provision. Covariates were chosen based on previously reported associations with CRP and availability (eg,

cholesterol was omitted from models due to incomplete coverage). We tested for differences in the slope of CRP trajectories by HIV category via interaction terms and for nonlinearities in average trajectory via transformations of age. We fit a separate model restricted to HIV+ samples to assess whether CD4+ T-cell count and HIV viral load were associated with CRP concentrations.

For analyses of extremely high CRP concentrations, we defined thresholds (>10 mg/L, approximately the 95th percentile, and >30 mg/L, approximately the 99th percentile) and compared frequencies of extremely high CRP values by HIV category. The time between samples (at minimum 6 months) was too great to determine whether any high CRP measurement represented a transient event or a more persistent inflammatory state. To test for predictors of extremely high CRP concentrations, including HIV status, we used multivariable logistic regression models adjusted for repeated measures by study participant. Statistical significance was assessed using $\alpha = .05$ for all analyses.

Results

Characteristics of Study Population

CRP measurements were available from 12 250 stored serum samples contributed by 2132 MACS participants from 1984 to 2014 (Table 1, Supplementary Table S1, Supplementary Figure 1). About half of these samples were contributed by participants with detectable HIV RNA, one-third by men with undetectable (suppressed) HIV RNA and one-sixth by HIV− men. The median duration of follow-up was 5.9 years (interquartile range: 2.0–11.5 years, maximum 29.4 years); 28% of participants had more than 10 years of follow-up. Participants contributed a median of 4 samples, with 28% contributing at least 7% and 13% contributing at least 10. Approximately half (51%) of participants contributed samples to more than 1 HIV study group, including 165 who contributed to all three. Men providing HIV+ suppressed samples were older than men providing samples for the other 2 groups ($p < .05$). Hepatitis C infection was twice as common among HIV− samples as among HIV+ samples ($p < .05$) per study design. Non-White race, obesity, cigarette smoking, and injection drug use were more common in the HIV− samples than in both groups of HIV+ samples ($p < .05$).

Distributions of CRP Concentrations

Median CRP concentrations were 0.9 mg/L in HIV− samples, 1.2 mg/L in HIV+ suppressed samples, and 1.2 mg/L in HIV+ detectable samples (Figure 1A). CRP concentrations increased with age in all 3 HIV categories (Figure 1B, Supplementary Table S2). Distributions of these concentrations among HIV+ detectable and HIV+ suppressed samples were nearly identical, with HIV+ detectable samples being the highest after age 40, and both were significantly higher than those in the HIV− group across all decades of age (from unadjusted linear mixed-effects models).

Factors Associated With CRP Values and Trajectories

A multivariable mixed-effects model was fit to the natural log of CRP measurements, incorporating age and the square of age, and allowing for differences in the effects of age by HIV category. Results are displayed in Table 2 and Figure 2. Age is centered at 45 years; for example, the estimated intercept term for HIV− men (0.061) implies a CRP concentration of 1.06 mg/L for an HIV− man at age 45 with reference values of covariates. Compared with HIV− men, men in both HIV+ categories had higher estimated CRP concentrations at age 45 (32% higher for HIV+ detectable men [95% CI: 26% to 50%]; 26% higher for HIV+ suppressed men [15% to 38%]).

Estimated CRP concentrations increased with age at a diminishing rate within each HIV category, peaking at 60 years in HIV− men, 67 years in HIV+ suppressed men, and 76 years in HIV+ detectable men. For HIV− men, the estimated linear component of change per decade was 17% (10% to 25%), and the estimated change per decade squared was −5% (−9% to −1%). The estimated linear component of change was significantly steeper in HIV+ detectable men (25% per decade, or an absolute difference of 8% [95% CI: 0.3% to 16%]) compared with HIV− men. HIV+ suppressed men also exhibited a faster linear increase than HIV− men, with a 5% absolute difference per decade, but this difference was not significant (95% CI: −3% to 13%). There were no statistically significant differences between groups in the age-squared term. The predicted CRP concentrations for HIV− men with reference values of covariates (Figure 2) were 0.62 mg/L at age 25, 1.06 mg/L at age 45, and 1.17 mg/L at age 65. For men with detectable HIV RNA, the corresponding figures were 0.79, 1.46, and 2.00 mg/L, and for men with suppressed HIV RNA, they were 0.74, 1.34, and 1.68 mg/L.

Table 1. Characteristics of Person-Visits in the Study Population

	HIV-Negative	HIV+ Suppressed	HIV+ Detectable	Total
Person-visits	1717	4075	6458	12 250
Men contributing person-visits*	738	1237	1413	2132
Visits per person†	2 (1, 4)	3 (1, 4)	3 (2, 6)	4 (3, 7)
Age in years†	42 (34, 50)	48 (42, 54)	41 (35, 48)	44 (37, 50)
HIV RNA copies/mL ($\log_{10}$)†	—	—	4.2 (3.3, 4.8)	4.2 (3.3, 4.8)
CD4+ cells/μL†	—	595 (428, 798)	469 (298, 677)	519 (345, 734)
CRP (mg/L)†	0.9 (0.4, 2.2)	1.2 (0.6, 2.9)	1.2 (0.6, 2.9)	1.2 (0.6, 2.8)
Non-White race	562 (33%)	1307 (20%)	1031 (25%)	2900 (24%)
Smoking at visit	669 (39%)	2206 (34%)	1117 (27%)	3992 (33%)
Injection drug use	85 (5%)	146 (2%)	84 (2%)	315 (3%)
Hepatitis C infection	263 (15%)	437 (7%)	298 (7%)	998 (8%)
Obesity	266 (15%)	608 (9%)	465 (11%)	1339 (11%)
Diabetes	124 (7%)	255 (4%)	370 (9%)	749 (6%)
Hypertension	373 (22%)	1369 (21%)	907 (22%)	2649 (22%)

Notes: CRP = C-reactive protein. Percentages and distributions apply to all samples within the specified group.

*Some men contributed visits to more than 1 category.

†Median (interquartile range).

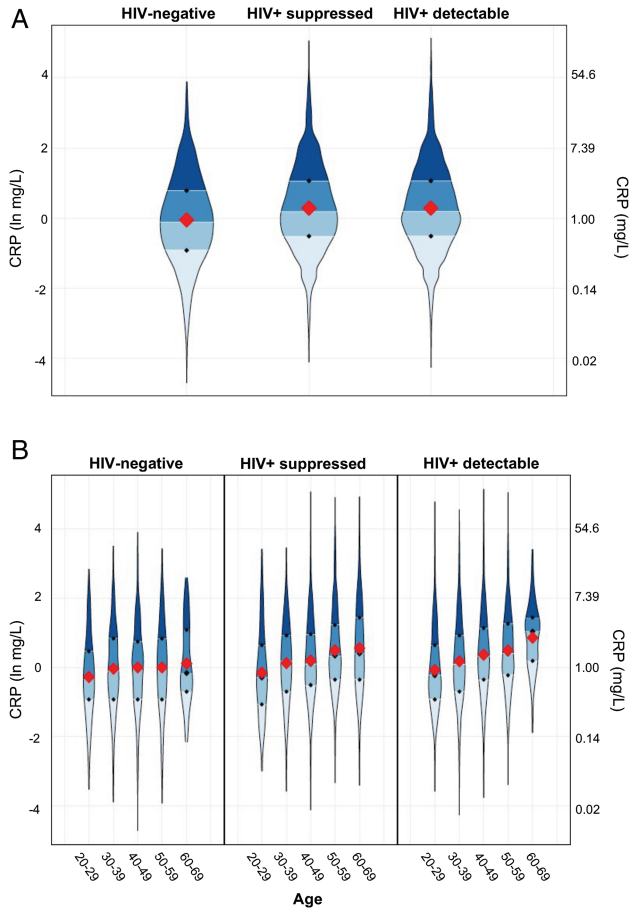

Figure 1. (A) C-reactive protein (CRP) distributions in samples by HIV category. (B) CRP distributions in samples by decade of age, stratified by HIV category. Data are shown as violin plots with quartiles shaded by color and width representing density. Black diamonds indicate 25th, 50th, and 75th percentiles. Red diamonds indicate means. Vertical labels on left indicate ln values, and labels on right indicate linear values.

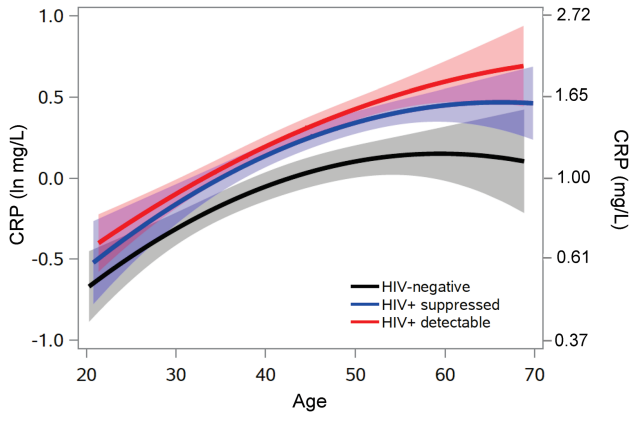

Figure 2. Predicted C-reactive protein (CRP) concentrations across age, by HIV category, from linear mixed-effects model. Transparent bands represent 95% confidence intervals. Predicted values are displayed for men with reference values of covariates in model (White race, nonsmoking, not using injection drugs, no HCV infection, no obesity, no diabetes, no hypertension).

There was no immediately apparent decline in CRP concentrations among the subset of participants (n = 514) who transitioned from the HIV+ detectable to the HIV+ suppressed group in visits within 2 years of one another; the median change was 0 mg/L (interquartile range: −0.8, 0.9). However, when we restricted the HIV+ suppressed group to men who were consistently suppressed (n = 1240 person-visits from men contributing at least 3 HIV+ samples after first becoming HIV+ suppressed, at least 75% of which had undetectable HIV RNA), the intercept and slope of serum CRP concentrations were lower than in the primary analysis, so that the estimated trajectory in this group was similar to that among the HIV− group (summary of sensitivity analyses in Supplementary Table S3; details of this analysis in Supplementary Table S4, Supplementary Figure 2).

As expected, HCV infection was associated with considerably lower CRP concentrations (−39%, 95% CI: −46% to −32%), and this was independent of age and HIV status. We fit a model with interaction terms between HCV infection status and age to test whether CRP trajectories differed depending on whether men were infected with HCV; the effect estimates were not statistically significant and did not support effect modification by HCV infection status. Obesity (30% higher, 95% CI: 20% to 40%) and cigarette smoking (17% higher, 95% CI: 11% to 25%) were associated with higher CRP concentrations independently of age and HIV status.

The median CRP concentration in the first HIV+ visit among men who seroconverted during follow-up (n = 497) was quite similar to that among HIV− samples (0.9 mg/L, interquartile range: 0.5, 2.1), contrary to what might be expected if these samples were provided during the acute HIV infection phase. Furthermore, when we excluded these samples from the primary analysis, results did not change appreciably (Supplementary Table S5, Supplementary Figure 3).

Among HIV+ samples, we fit a linear mixed-effects model with a quadratic function of age to test for associations between CRP

Table 2. Fixed Effect Estimates From Linear Mixed-Effects Model of Natural Log of C-Reactive Protein (mg/L) Concentrations OverTime

		Coefficient	95% LL	95% UL
HIV− (ref.)	Intercept (age 45, ref.)	0.061	−0.032	0.154
	10 y of age (ref.)	**0.158**	0.095	0.221
	Square of age term (ref.)	**−0.054**	−0.098	−0.011
HIV+, suppressed	Effect on intercept term	**0.232**	0.138	0.325
	Effect on 10 y of age term	0.048	−0.028	0.125
	Effect on squared age term	0.008	−0.048	0.064
HIV+, detectable	Effect on intercept	**0.319**	0.232	0.405
	Effect on 10 y of age term	**0.075**	0.003	0.146
	Effect on squared age term	0.016	−0.034	0.066
Other fixed effects	Non-White race	0.056	−0.032	0.144
	Current smoking	**0.161**	0.102	0.219
	Injection drug use	0.046	−0.076	0.169
	Current hepatitis C infection	**−0.500**	−0.618	−0.382
	Obesity	**0.261**	0.182	0.340
	Diabetes	0.069	−0.023	0.162
	Hypertension	**0.045**	0.000	0.091

Notes: 95% LL = lower limit of 95% confidence interval, 95% UL = upper limit of 95% confidence interval; CRP = C-reactive protein. Bold indicates $p < .05$.

concentrations and continuous measures of HIV disease status (HIV viral load and CD4+ T-cell counts). We excluded 551 samples (4%) due to missing CD4+ T-cell count or HIV viral load. Results are shown in Supplementary Table S6. As in the previous model, CRP concentrations increased at a diminishing rate with age. Lower CD4+ cell counts were associated with higher CRP concentrations (4% higher CRP per 100 fewer CD4+ cells/μL, 95% CI: 3% to 5%); CRP concentrations and log HIV viral load were positively associated (0.8% increase per $\log_{10}$ copies of HIV RNA), but the 95% confidence interval included the null (−0.0% to 1.6%).

Extremely High CRP Concentrations

Extremely high CRP concentrations, defined as >10 mg/L, were observed in 524 samples, with a few (n = 10) measuring over 100 mg/L. Eighty-one percent of study participants had no samples with extremely high CRP concentrations, whereas some men had up to 8 such values, though the total number of samples available for each individual varied considerably. Factors associated with a given sample having an extremely high CRP concentration are given in Table 3. Significantly higher odds of an extremely high CRP concentration were estimated for both HIV+ detectable (odds ratio [OR]: 1.74, 95% CI: 1.22 to 2.48) and HIV+ suppressed samples (OR: 1.50, 95% CI: 1.04 to 2.15) relative to HIV− samples, and for those who previously had an extremely high CRP measurement relative to those who had not (OR: 2.78, 95% CI: 2.14 to 3.62). Additional statistically significant predictors of extremely high CRP values were older age, non-White race, and smoking.

When we considered the higher threshold of >30 mg/L (observed in 129 samples, Table 3), larger estimated ORs were obtained comparing HIV+ detectable and HIV+ suppressed samples to HIV− samples, although the estimate for HIV+ suppressed samples was not statistically significant. Again, having a previous CRP measurement of this magnitude and older age were statistically significant predictors of extremely high CRP concentrations at this higher threshold. To evaluate the influence of these extremely high CRP values on our primary results, we fit our linear mixed-effects model after excluding CRP values > 30 mg/L; results were very similar to those obtained without this exclusion (Supplementary Table S7, Supplementary Figure 4).

Discussion

This study is, to the best of our knowledge, the first to detail long-term trajectories of CRP in a population of people living with HIV. It is also one of the largest analyses of CRP, comprising 12 250 measurements in 2132 men over a span of 30 years, including up to 4 measurements in HIV− men. In contrast to most earlier studies, in which CRP was measured at only 1 or 2 time points, more than a quarter of participants contributed 7 visits or more. We found that CRP concentrations increased with age in all 3 groups defined by HIV status (ie, HIV−, HIV+ suppressed, HIV+ detectable) and that the magnitude of this increase was large, with concentrations increasing by more than 60% in each group from age 30 to 60. Consistent with previous evidence, HIV infection was strongly associated with higher CRP concentrations independently of age (5,32). In a novel finding, estimated age-related increases were steeper among men living with HIV relative to HIV− men. Notably, we observed a flattening of CRP trajectories with age regardless of HIV status, but this leveling off occurred later among both HIV+ groups.

Among HIV+ samples, lower CD4+ cell count was significantly associated with higher CRP, which is consistent with the previously reported result that HIV progression is associated with greater inflammation (34). As expected, CRP concentrations were positively associated with smoking, obesity, and hypertension and negatively with HCV infection. Men with detectable HIV RNA at a given study visit had an estimated 74% higher odds of having a CRP concentration greater than 10 mg/L—and nearly 3 times the odds of having a CRP measurement greater than 30 mg/L—relative to HIV− men. This may reflect the higher risks of infection and other acute inflammatory states associated with chronic HIV replication and impaired immune function.

These results are concordant with the hypothesis that increased inflammation is a feature of aging and that HIV infection may exacerbate this aspect of aging (1–3); however, the question of whether HIV infection causes accelerated physical aging is beyond the scope of this article. The similarity of estimated CRP trajectories overall between visits with detectable and suppressed HIV RNA highlights the need to develop treatments and promote behavioral modifications to reduce the chronic low-level inflammation associated with treated HIV infection. Notably, however, when we restricted the HIV+ suppressed group to visits only from men who achieved a consistent state of suppression over time, we found that the estimated CRP trajectory was more similar to that observed among HIV− men; this result suggests that sustained viral suppression may lower chronic inflammation.

A primary strength of the study is a cardinal characteristic of the MACS cohort in general: the ability to compare results between a large number of men living with HIV and HIV− men from a similar source

Table 3. Odds Ratios for Extremely High C-Reactive Protein Concentrations

	Defined as >10 mg/L			Defined as >30 mg/L		
	OR	95% LL	95% UL	OR	95% LL	95% UL
HIV− (ref.)	—	—	—	—	—	—
HIV+, suppressed	**1.50**	1.04	2.15	1.88	0.84	4.20
HIV+, detectable	**1.74**	1.22	2.48	**2.84**	1.29	6.25
Previous extremely high CRP	**2.78**	2.14	3.62	**5.55**	3.43	8.98
10 y of age	**1.27**	1.14	1.42	**1.39**	1.15	1.68
Non-White race	**1.34**	1.08	1.65	1.42	0.94	2.16
Current smoking	**1.24**	1.02	1.50	0.88	0.61	1.26
Injection drug use	0.93	0.52	1.67	0.94	0.29	3.01
Current hepatitis C infection	0.89	0.62	1.28	1.12	0.58	2.17
Obesity	1.07	0.80	1.43	0.51	0.26	1.03
Diabetes	1.12	0.76	1.65	1.18	0.61	2.27
Hypertension	1.03	0.84	1.28	1.15	0.77	1.71

Notes: 95% LL = lower limit of 95% confidence interval; 95% UL = upper limit of 95% confidence interval; CRP = C-reactive protein; OR = odds ratio. Bold indicates $p < .05$.

population over a long time span. This comparison allows inference about the effects of chronic HIV infection and its treatment, independently of what may be expected as men age. The uniformity of CRP measurement is an additional advantage. CRP is also known to be highly stable in storage at −80°C for over a decade, and CRP concentrations exhibit low intraindividual variability over short durations (27,35). However, the study also has some limitations. Irregular and relatively long (~6 months) intervals between measurements present challenges to interpretation, as does the lack of data on comorbidities that may acutely affect single CRP measurements (eg, a recent mild illness). Results may have been subject to some survivor bias, as participants with morbidities related to either HIV or aging may have been less likely to contribute samples over time. The number of samples from HIV− men was smaller than that from HIV+ men, although it was not small compared with previous longitudinal studies of CRP. The study period does not include modern cART regimens such as those containing integrase strand transfer inhibitors, which also limits generalizability. As this was an observational study, we may not have adequately adjusted for differences across HIV groups that were related to CRP concentrations. Finally, this study included only men; studies of CRP trajectories in women are needed.

CRP is commonly measured in clinical settings and is a known predictor of morbidity and mortality. Better understanding of its age-related dynamics in HIV infection will provide context for observed departures from expected trajectories. A next step is to estimate how CRP trajectories and clinical outcomes are related to one another among PLWH. The detailed picture presented here of how CRP changes with age in men, and how this is associated with HIV status, provides a necessary first step to this end.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None declared.

References

1. Pathai S, Bajillan H, Landay AL, High KP. Is HIV a model of accelerated or accentuated aging? *J Gerontol A Biol Sci Med Sci*. 2014;69(1):833–842. doi:10.1093/gerona/glt168
2. Önen NF, Overton ET. A review of premature frailty in HIV-infected persons; another manifestation of HIV-related accelerated aging. *Curr Aging Sci*. 2011;4(1):33–41. doi:10.2174/1874612811104010033
3. Horvath S, Levine AJ. HIV-1 infection accelerates age according to the epigenetic clock. *J Infect Dis*. 2015;212:1563–1573. doi:10.1093/infdis/jiv277
4. Margolick JB, Ferrucci L. Accelerating aging research: how can we measure the rate of biologic aging? *Exp Gerontol*. 2015;64:78–80. doi:10.1016/j.exger.2015.02.009
5. Wada NI, Jacobson LP, Margolick JB, et al. The effect of HAART-induced HIV suppression on circulating markers of inflammation and immune activation. *AIDS*. 2015;29:463–471. doi:10.1097/QAD.0000000000000545
6. Wada NI, Bream JH, Martínez-Maza O, et al. Inflammatory biomarkers and mortality risk among HIV-suppressed men: a multisite prospective cohort study. *Clin Infect Dis*. 2016;63:984–990. doi:10.1093/cid/ciw409
7. Lau B, Sharrett AR, Kingsley LA, et al. C-reactive protein is a marker for human immunodeficiency virus disease progression. *Arch Intern Med*. 2006;166:64–70. doi:10.1001/archinte.166.1.64
8. Thompson D, Pepys MB, Wood SP. The physiological structure of human C-reactive protein and its complex with phosphocholine. *Structure*. 1999;7(2):169–177. doi:10.1016/S0969-2126(99)80023-9
9. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *J Clin Invest*. 2003;111:1805–1812. doi:10.1172/JCI18921
10. Vermeire S, Van Assche G, Rutgeerts P. Laboratory markers in IBD: useful, magic, or unnecessary toys? *Gut*. 2006;55:426–431. doi:10.1136/gut.2005.069476
11. Furman D, Campisi J, Verdin E, et al. Chronic inflammation in the etiology of disease across the life span. *Nat Med*. 2019;25:1822–1832. doi:10.1038/s41591-019-0675-0
12. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation*. 2003;107:363–369. doi:10.1161/01.cir.0000053730.47739.3c
13. Ridker PM, Rifai N, Pfeffer MA, Sacks F, Braunwald E. Long-term effects of pravastatin on plasma concentration of C-reactive protein. The Cholesterol and Recurrent Events (CARE) Investigators. *Circulation*. 1999;100:230–235. doi:10.1161/01.cir.100.3.230
14. Danesh J, Wheeler JG, Hirschfield GM, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med*. 2004;350:1387–1397. doi:10.1056/NEJMoa032804
15. Zacho J, Tybjaerg-Hansen A, Jensen JS, Grande P, Sillesen H, Nordestgaard BG. Genetically elevated C-reactive protein and ischemic vascular disease. *N Engl J Med*. 2008;359:1897–1908. doi:10.1056/NEJMoa0707402
16. Tang Y, Fung E, Xu A, Lan HY. C-reactive protein and ageing. *Clin Exp Pharmacol Physiol*. 2017;44(suppl 1):9–14. doi:10.1111/1440-1681.12758
17. McEniery Carmel M, Spratt M, Munnery M, et al. An analysis of prospective risk factors for aortic stiffness in men. *Hypertension*. 2010;56(1):36–43. doi:10.1161/HYPERTENSIONAHA.110.150896
18. Soysal P, Stubbs B, Lucato P, et al. Inflammation and frailty in the elderly: a systematic review and meta-analysis. *Ageing Res Rev*. 2016;31:1–8. doi:10.1016/j.arr.2016.08.006
19. Margolick JB, Bream JH, Martínez-Maza O, et al. Frailty and circulating markers of inflammation in HIV+ and HIV− men in the Multicenter AIDS Cohort Study. *J Acquir Immune Defic Syndr*. 2017;74:407–417. doi:10.1097/QAI.0000000000001261
20. Zacho J, Tybjaerg-Hansen A, Nordestgaard BG. C-reactive protein and all-cause mortality – the Copenhagen City Heart Study. *Eur Heart J*. 2010;31:1624–1632. doi:10.1093/eurheartj/ehq103

21. Zhuang Q, Shen C, Chen Y, et al. Association of high sensitive C-reactive protein with coronary heart disease: a Mendelian randomization study. *BMC Med Genet*. 2019;20:170. doi:10.1186/s12881-019-0910-z
22. Shanahan L, Freeman J, Bauldry S. Is very high C-reactive protein in young adults associated with indicators of chronic disease risk? *Psychoneuroendocrinology*. 2014;40:76–85. doi:10.1016/j.psyneuen.2013.10.019
23. Mac Giollabhui N, Ellman LM, Coe CL, Byrne ML, Abramson LY, Alloy LB. To exclude or not to exclude: considerations and recommendations for C-reactive protein values higher than 10 mg/L. *Brain Behav Immun*. 2020;87:898–900. doi:10.1016/j.bbi.2020.01.023
24. Woloshin S, Schwartz LM. Distribution of C-reactive protein values in the United States. *N Engl J Med*. 2005;352:1611–1613. doi:10.1056/NEJM200504143521525
25. Ford ES, Giles WH, Myers GL, Mannino DM. Population distribution of high-sensitivity C-reactive protein among US men: findings from National Health and Nutrition Examination Survey 1999–2000. *Clin Chem*. 2003;49:686–690. doi:10.1373/49.4.686
26. Puzianowska-Kuźnicka M, Owczarz M, Wieczorowska-Tobis K, et al. Interleukin-6 and C-reactive protein, successful aging, and mortality: the PolSenior study. *Immun Ageing*. 2016;13:21. doi:10.1186/s12979-016-0076-x
27. Chen TH, Gona P, Sutherland PA, et al. Long-term C-reactive protein variability and prediction of metabolic risk. *Am J Med*. 2009;122:53–61. doi:10.1016/j.amjmed.2008.08.023
28. Beatty Moody DL, Chang Y, Brown C, Bromberger JT, Matthews KA. Everyday discrimination and metabolic syndrome incidence in a racially/ethnically diverse sample: study of women's health across the nation. *Psychosom Med*. 2018;80:114–121. doi:10.1097/PSY.0000000000000516
29. Friedlander Y, Kark JD, Sinnreich R, Tracy RP, Siscovick DS. Fibrinogen and CRP in Israeli families: genetic and environmental sources of concentrations and longitudinal changes. *Atherosclerosis*. 2006;189:169–177. doi:10.1016/j.atherosclerosis.2005.11.030
30. Kaslow RA, Ostrow DG, Detels R, Phair JP, Polk BF, Rinaldo CR Jr. The Multicenter AIDS Cohort Study: rationale, organization, and selected characteristics of the participants. *Am J Epidemiol*. 1987;126:310–318. doi:10.1093/aje/126.2.310
31. Bhuiyan AR, Mitra AK, Ogungbe O, Kabir N. Association of HCV infection with C-reactive protein: National Health and Nutrition Examination Survey (NHANES), 2009–2010. *Diseases*. 2019;7(1):25. doi:10.3390/diseases7010025
32. Reingold J, Wanke C, Kotler D, et al. Association of HIV infection and HIV/HCV coinfection with C-reactive protein levels: the fat redistribution and metabolic change in HIV infection (FRAM) study. *J Acquir Immune Defic Syndr*. 2008;48:142–148. doi:10.1097/QAI.0b013e3181685727
33. Salter ML, Lau B, Mehta SH, Go VF, Leng S, Kirk GD. Correlates of elevated interleukin-6 and C-reactive protein in persons with or at high risk for HCV and HIV infections. *J Acquir Immune Defic Syndr*. 2013;64:488–495. doi:10.1097/QAI.0b013e3182a7ee2e
34. Redd AD, Eaton KP, Kong X, et al. C-reactive protein levels increase during HIV-1 disease progression in Rakai, Uganda, despite the absence of microbial translocation. *J Acquir Immune Defic Syndr*. 2010;54:556–559. doi:10.1097/QAI.0b013e3181e0cdea
35. Doumatey AP, Zhou J, Adeyemo A, Rotimi C. High sensitivity C-reactive protein (Hs-CRP) remains highly stable in long-term archived human serum. *Clin Biochem*. 2014;47:315–318. doi:10.1016/j.clinbiochem.2013.12.014