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Inflammation and Mortality in HIV-infected Adults: Analysis of the FRAM Study Cohort

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Abstract

Objective—To determine the association of inflammatory markers, fibrinogen and C-reactive protein (CRP), with 5-year mortality risk.

Methods—Vital status was ascertained in 922 HIV-infected participants from the Study of Fat Redistribution and Metabolic Change in HIV infection. Multivariable logistic regression estimated odds ratios (OR) after adjustment for demographic, cardiovascular and HIV-related factors.

Results—Over a 5-year period, HIV-infected participants with fibrinogen levels in the highest tertile(>406mg/dL) had 2.6-fold higher adjusted odds of death than those with fibrinogen in the lowest tertile(<319mg/dL). Those with high CRP(>3mg/L) had 2.7-fold higher adjusted odds of death than those with CRP<1mg/L. When stratified by CD4 count category, fibrinogen (as a linear variable) remained independently associated [OR(95% confidence intervals) per 100mg/dL increase in fibrinogen: 1.93(1.57,2.37);1.43(1.14,1.79);1.43(1.14,1.81);and 1.30(1.04,1.63) for CD4 <200,200–350,>350–500, and >500cells/μL, respectively. Higher CRP also remained associated with higher odds of death overall and within each CD4 subgroup.

Conclusion—Fibrinogen and CRP are strong and independent predictors of mortality in HIV-infected adults. Our findings suggest that even in those with relatively preserved CD4 counts >500cells/μL, inflammation remains an important risk factor for mortality. Further investigation should determine whether interventions to reduce inflammation might decrease mortality risk in HIV-infected individuals.

Keywords

HIV; inflammation; C-reactive protein; fibrinogen; mortality

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INTRODUCTION

Despite marked reductions in HIV-related mortality since the introduction of highly active antiretroviral therapy (HAART) [1], mortality in HIV-infected persons remains higher than in the general population [2–5]. We previously reported that HIV infection was associated with 3-fold higher odds of death even after controlling for demographic and traditional cardiovascular disease (CVD) risk factors [5]. Whether inflammation (which is thought to be a consequence of chronic infection and immune activation) contributes to death in HIV-infected individuals, beyond demographic and CVD risk factors, is the topic of current investigation.

To our knowledge, only one published study has examined the association of inflammatory markers with mortality in HIV-infected individuals in the HAART era [6]. That study from the Strategies for Management of Anti-Retroviral Therapy (SMART) trial found a strong association of IL-6 (an inflammatory cytokine), D-dimer (an inflammatory protein involved in the clotting cascade), and C-reactive protein (CRP) (a proinflammatory biomarker) with mortality. We recently found that HIV infection was associated with higher levels of fibrinogen [7] (another inflammatory biomarker in the clotting cascade) and CRP [8] than controls. Both fibrinogen and CRP have been associated with increased vascular and non-vascular mortality in the general population [9–11].

Herein, we evaluated the association of fibrinogen and CRP with mortality in a geographically and ethnically diverse cohort of HIV-infected individuals in clinical care in the United States. In order to assess the role of immunosuppression severity on the association of inflammation with mortality, we further stratified HIV-infected individuals into four CD4 count risk categories. We hypothesized that inflammation would be independently associated with mortality in HIV infection.

METHODS

Study Population

Between June 2000 and September 2002, 1183 HIV-infected men and women from 16 geographically diverse sites were enrolled in the study of Fat Redistribution and Metabolic Change in HIV infection (FRAM), with a follow-up exam conducted approximately five years later (FRAM2). HIV-infected participants in FRAM were nationally representative of HIV-infected patients in care [12]. The study design, recruitment methods and data collection procedures for the entire FRAM cohort have been described elsewhere [12], and retention outcomes for participants enrolled in the first exam have been reported [5]. At the second exam, 922 HIV-infected participants were known to be alive or known to be dead; vital status could not be determined for the remaining 261 HIV-infected participants. Linkage to the National Death Index was not possible because of institutional review board and patient confidentiality issues. Baseline characteristics of those with unknown vital status and those who were alive at the second FRAM exam appeared more similar to each other than to those who were dead. For those with unknown vital status and those who were alive at the second exam, median age was 41.0 and 42.5 years, respectively compared to 44.5 for those who died. Similarly, the proportion African-American was 34% and 39%, respectively compared to 51% for those who died; the proportion reporting current smoking was 46% and 38% vs. 61%. Among the HIV-related factors, median CD4 count was 338 and 389 vs. 189 cells/ml for those who died; median CRP was 1.6 and 1.7 vs. 2.8 mg/L and median fibrinogen was 356 and 355 vs. 443 mg/dL. The institutional review boards at all sites approved the protocols for both FRAM exams.

Study Measurements

As described previously [7,8], fibrinogen and CRP was quantitatively measured in frozen plasma and sera, respectively (i.e. stored at -70°C and not previously thawed) from the first FRAM exam using the BNII nephelometer from Dade Behring (Deerfield, IL), which utilizes a particle enhanced immunonephelometric assay. The intra-assay and inter-assay coefficient of variations for fibrinogen were 2.7% and 2.6%, respectively. The lower limit of detection for the ultrasensitive CRP assay used in FRAM was 0.16mg/L. The inter-assay coefficient of variations for CRP ranged from 3.7 to 4.5%.

FRAM also measured cystatin C in frozen sera using the BNII nephelometer [13] and estimated glomerular filtration rate (eGFR) based on cystatin C calculated using the CKD Epidemiology Collaboration Equation: $[\text{eGFR} = 76.7 \times \text{cystatin C}^{-1.19}]$ [14]. Urinalysis was also performed to determine microalbuminuria [positive urine dipstick (1+ or greater) or a urine albumin to urine creatinine ratio greater than 30 mg/g] in real-time [15].

Predictors of mortality

Fibrinogen was studied both as a continuous variable (per 100mg/dL increase) and as a categorical variable determined by tertiles of fibrinogen levels. CRP was studied both as a continuous variable after log transformation ($\log_2$) and as a categorical variable based on the Center for Disease Control (CDC)/American Heart Association (AHA) guidelines [16]: low risk <1 mg/L, average risk 1–3 mg/L, and high risk >3 mg/L. Demographic characteristics included self-reported age at baseline, sex, and race. Additional candidate predictors included cardiovascular disease risk factors at baseline: diabetes (hypoglycemic medication use or fasting glucose ≥ 126), smoking status (current, past, never; pack years), waist circumference, systolic blood pressure, diastolic blood pressure, HDL and non-HDL cholesterol, and medication use (anti-hypertensives and hypolipidemics). Candidate predictors related to HIV infection included: HIV RNA level at baseline, CD4 count at baseline, self-reported duration of HIV, AIDS [defined as CD4 count <200 or AIDS-defining opportunistic infection (OI)/malignancy (OM)] at baseline, active hepatitis C virus (HCV) infection (defined as a detectable HCV RNA at baseline), and lean body mass by MRI. In addition, use of each antiretroviral (ARV) drug and class was evaluated both by ever use of the drug or class and by total duration of use.

Statistical Analysis

Multivariable logistic regression analysis was used to investigate whether there was an independent association of fibrinogen and CRP with five-year mortality risk in HIV-infected participants. Because the exact dates of death were unknown, those who died provided left-censored observations, meaning that death was only known to have occurred sometime before the contact attempt at approximately five years of follow-up. We therefore used logistic regression rather than Cox proportional hazards regression as our primary analysis, with an offset term to account for variation in follow-up time. Follow-up time was defined as elapsed time from baseline to follow-up exam or last contact. For deceased subjects, the follow-up time was defined as 4.6 years (the median follow-up time for those with known vital status).

Covariates included in the multivariable analysis are the baseline demographic, cardiovascular disease risk factors, and HIV-related factors listed above. To ensure that models were not overfit, we also built more parsimonious models using a backward stepwise procedure. Similar analyses were conducted separately within HIV-infected participants who had different baseline CD4 counts (<200 , 200 to 350, >350 to 500, and >500) using the same models. We stratified by CD4 count and not by presence or absence of detectable HIV RNA, because we previously demonstrated that after adjustment for demographic and traditional cardiovascular risk factors, detectable HIV RNA was no longer associated with mortality risk [5]. Age-

standardized mortality rates were calculated within strata of CD4, fibrinogen, and CRP using fitted values from the logistic regression models, with estimates standardized to the approximate mean age of the overall cohort at enrollment (40 years).

Multiple imputation using the Markov chain Monte Carlo method for arbitrary missing data was used to impute missing covariates [17]. To account for those with unknown vital status, we performed analyses using an inverse probability weighting approach [18,19] by modeling each participant's probability of having a known death status. The inverse of this probability was then used as a weight (applied to persons with known vital status) in the logistic regression analysis of death. We conducted additional analyses to assess the potential bias introduced to our results by limited vital status data. First, we compared main model results without the application of inverse probability weights for vital status. Second, we repeated analyses assuming that all participants who were lost to follow-up were alive. Finally, we also performed analyses excluding those with unknown vital status. All analyses were conducted using the SAS system, version 9.2 (SAS Institute, Inc., Cary, NC).

RESULTS

Demographic and baseline clinical characteristics of the 922 HIV-infected participants stratified by tertiles of fibrinogen levels are shown in Table 1. HIV-infected participants with fibrinogen levels in the highest tertile at the baseline exam were older (median: 43.3 vs. 41.1 years), more often African American (50% vs. 29%), had lower high density lipoprotein (HDL) (median: 38.9 vs. 42.1mg/dL), and higher total cholesterol (median: 196.1 vs. 187.2mg/dL) and CRP levels (median: 3.30 vs. 1.12mg/L) than those with fibrinogen levels in the lower tertiles. Among the HIV-related factors, HIV RNA levels were higher (median: 600 vs. 400 copies/ml) and CD4 counts were lower (median: 329 vs. 388 cells/ml) in those with fibrinogen levels in the highest tertile. Fibrinogen and CRP were moderately correlated (Spearman rank correlation coefficient: 0.43).

Association of Fibrinogen and CRP with Mortality in HIV-infection

Over the five-year period, HIV-infected participants with fibrinogen levels in the highest tertile had an unadjusted mortality rate of 24.7% compared to 9.7% and 7.4% in those with fibrinogen in the middle and low tertiles, respectively. HIV-infected participants with high CRP (>3 mg/L) also had a higher unadjusted mortality rate of 19.3% compared to 14.4% in those with CRP 1–3 mg/L and 7.3% in those with CRP <1 mg/dL (Table 2). Age-standardized mortality rates showed a similar increase across these fibrinogen and CRP categories (Figure 1). Mortality rates were highest in those for whom both fibrinogen and CRP were high.

After adjustment for demographic, CVD and HIV-related factors (Table 2), those with fibrinogen in the highest tertile had a 3.4-fold higher odds of death compared with those in the lowest tertile. Similarly, high CRP (>3 mg/L) was associated with a 3.7-fold higher odds of death compared to those with low CRP (<1 mg/L) (Table 2). When fibrinogen and CRP were simultaneously included in the multivariable model, both high fibrinogen and high CRP remained independently associated with a 2.6 and 2.7-fold higher odds of death compared with those in the lowest fibrinogen and CRP categories, respectively.

We observed similar results when fibrinogen and CRP levels were assessed as continuous measures. Fibrinogen and CRP were individually associated with higher odds of death (OR = 1.70 per 100 mg/dL increase in fibrinogen, 95% CI: 1.43, 2.02; and OR = 1.36 per doubling of CRP, 95% CI: 1.22, 1.52, respectively). When fibrinogen and CRP were included jointly in the multivariable model, both remained independently associated with higher odds of death (OR = 1.48 per 100 mg/dL increase in fibrinogen, 95% CI: 1.21, 1.81; and OR = 1.20 per doubling of CRP, 95% CI: 1.06, 1.37, respectively), although associations were attenuated.

There was some evidence for a fibrinogen and CRP interaction, although it did not reach statistical significance ($p=0.071$). As illustrated in Figure 1, effects of higher fibrinogen and CRP did not appear to be additive when both were elevated. Interactions of fibrinogen and CRP with CD4 and HIV RNA level appeared to be much weaker (all $p>0.37$).

In all sensitivity analyses, point estimates for markers of inflammation were very similar to main model results (data not shown).

Association of Fibrinogen and CRP with Mortality stratified by CD4 category

We next examined the role of CD4 risk category (<200, 200–350, >350–500, and >500) on the association of fibrinogen and CRP with mortality by analyzing fibrinogen and CRP as continuous measures. Fibrinogen and CRP were independently associated with higher odds of death in every CD4 category, after adjustment for demographic, CVD, and HIV-related factors (Table 3). When fibrinogen and CRP were simultaneously included in the multivariable model, each remained associated with higher odds of death. The OR for the associations of fibrinogen and CRP with mortality were largest in those with CD4 <200 and smallest in those with CD4 >500, although the tests for trend were not statistically significant (fibrinogen: $p=0.38$, CRP: $p=0.90$). Even in those with CD4 >500, a substantial proportion had inflammation (26% with fibrinogen levels in the highest tertile and 36% with high CRP >3 mg/L). There was little difference in CRP levels by CD4 count category. The median and interquartile ranges by CD4 category <200, 200–350, 350–500, and >500 were: 1.80 (0.82–4.14), 1.88 (0.83–3.99); 1.72 (0.79–3.65), and 1.82 (0.69–4.31), respectively; $p=0.88$. The median and interquartile ranges for fibrinogen was higher in those with CD4<200 compared to those with CD4 200–350, 350–500, and >500 [379 (316–471), 355 (299–422), 353 (283–439), and 355 (286–416), respectively; $p=0.005$].

After further adjustment for markers of renal disease (i.e. microalbuminuria and estimated glomerular filtration rate based on cystatin C), fibrinogen and CRP remained associated with higher odds of overall death and death in every CD4 category (data not shown).

DISCUSSION

In our nationally representative cohort of HIV-infected individuals in the recent HAART era, we found that elevated levels of fibrinogen and CRP were strong and independent predictors of five-year mortality risk. Our findings suggest an important role for inflammation in mortality risk beyond demographic, cardiovascular, and HIV-related factors. Furthermore, when HIV-infected participants were stratified by degree of immunosuppression, fibrinogen and CRP were independently associated with higher odds of death in every CD4 category. While fibrinogen and CRP appeared to have stronger associations in those with low CD4 count, the associations remained even in the highest CD4 category.

Our findings support the observations from the SMART trial [6], which reported an association of IL-6, D-dimer, and CRP with mortality in HIV-infected participants from the recent HAART era. Their case control analysis however, included only 255 HIV-infected participants; the majority of whom had relatively preserved CD4 counts (median baseline CD4 count >500). While our study did not test the association of IL-6 and D-dimer with mortality, we found that fibrinogen (also an inflammatory marker in the clotting cascade) was strongly associated. Our results are also consistent with a study from the pre-HAART era that found an association between CRP and all-cause mortality [20]. That study was limited to HIV-infected women from Brooklyn, New York with a median CD4 count of 290. Taken together, these observations suggest that inflammation is an important risk factor for mortality in HIV-infected persons.

A strength of our study was the wide spectrum of CD4 levels in our participants, which allowed us to examine the effect of immunosuppression severity on the association of inflammation with mortality. As expected, we found that the OR for mortality associated with fibrinogen and CRP was greatest in magnitude for those with CD4 <200. However, more important is our finding that higher fibrinogen and CRP levels remained associated with increased mortality risk in participants with CD4 >500. The lack of a substantial interaction of fibrinogen and CRP with CD4 also strengthened our hypothesis that the association of inflammation with mortality is independent of the absolute CD4 count. These findings could suggest that the CD4 cells remain immunologically activated despite CD4 cell restoration. The subsequent persistent inflammatory state could contribute to non-HIV-related comorbidities such as liver and cardiovascular disease, which have been reported as the leading causes of non-HIV-related death in the HAART era [4,21–24]. While we did observe that the OR was greater for those with CD4 count <200, this could be due to other factors such as infections or malignancies that are a consequence of a low CD4 count that may increase inflammation, for which we were not able to adequately adjust. Interestingly, a recent study found that early initiation of antiretroviral therapy (before the CD4 count fell below 500) improved survival in HIV-infected individuals [25]. It is not yet known whether reduction of inflammation was a mechanism for the beneficial effect of antiretroviral therapy. Whether or not levels of fibrinogen and CRP might be an additional prognostic marker warrants investigation.

The novel association of fibrinogen with all-cause mortality in HIV-infected individuals is also noteworthy. Fibrinogen is a coagulation protein that is thought to play a major role in platelet aggregation and thus vascular-related morbidity and mortality. However, a large meta-analysis of HIV-uninfected individuals found moderately strong associations between plasma fibrinogen levels and non-vascular mortality (mainly cancer), in addition to coronary heart disease, stroke, and other vascular mortality [10]. Interestingly, fibrinogen is increased in smokers (who are at risk for vascular and non-vascular morbidities) and has been shown to decrease with cessation of smoking [26]. Smoking is highly prevalent in HIV-infected individuals and is a key predictor of mortality risk in HIV infection [5]. Nevertheless, after controlling for cardiovascular risk factors including smoking, fibrinogen remained independently associated with mortality in HIV-infected individuals. The relationship of fibrinogen levels to D-dimer levels must also be explored; unfortunately we were unable to assay D-dimer and IL-6 levels on our participants.

There are limitations to our study. First, vital status could not be determined in 23% of the HIV-infected participants who could not be contacted, which may have led to an underestimation of the mortality rate. We therefore used a multiple imputation and inverse probability weighting approach to model the participant's probability of having a known death status. Additional sensitivity analyses produced results that were similar to our primary modeling approach. Second, we did not have information regarding the cause of death and were therefore unable to discern whether the independent association of fibrinogen and CRP with mortality in HIV-infected individuals was due to cardiovascular or non-cardiovascular deaths. Finally, as with all observational studies, our findings are subject to possible unmeasured confounding.

We conclude that elevated levels of fibrinogen and CRP are strong and independent predictors of all-cause mortality in HIV-infected adults. Our findings that fibrinogen and CRP remained associated with higher odds of death regardless of the degree of immunosuppression suggests that inflammation remains an important factor even in those with relatively preserved CD4 cells. Investigation is needed to determine whether interventions to reduce fibrinogen and CRP levels might decrease mortality risk in HIV-infected individuals.

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Appendix

Conflicts of Interest

None.

Role of the Funder

The funder played no role in the conduct of the study, collection of the data, management of the study, analysis of data, interpretation of the data or preparation of the manuscript. A representative of the funding agent participated in planning the protocol. As part of the standard operating procedures of CARDIA, the manuscript was reviewed at the NHLBI, but no revisions were requested.

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Figure 1.
Age-standardized mortality rates* in HIV-infected patients, stratified by fibrinogen and CRP levels.

*Estimates standardized to 40 years (the approximate mean age of the overall cohort at enrollment)

TABLE 1

Baseline characteristics of HIV-infected participants by fibrinogen tertile*

	Fibrinogen			
	< 319 mg/dL (n=313)	319–406 mg/dL (n=306)	> 406 mg/dL (n=303)	P-value
Age (y)	41.1 (35.8–45.9)	41.4 (36.4–47.6)	43.3 (37.1–49.7)	0.008
Gender				
Female	26%	30%	34%	0.29
Male	74%	70%	66%	
Race				
African-American	29%	39%	50%	0.018
Caucasian	57%	50%	36%	
Other	14%	11%	14%	
Diabetes	6.7%	8.4%	10.9%	0.35
Smoking Status				
Current	40%	41%	44%	0.89
Past	24%	23%	24%	
Never	37%	36%	32%	
Antihypertensive use	16%	22%	28%	0.029
ACE-I use	6.1%	7.9%	13%	0.33
Hyperlipidemia Treatment	12%	19%	16%	0.012
Systolic BP (mmHg)	114.8 (106.3–122.2)	116.3 (106.9–124.5)	114.5 (105.0–124.0)	0.36
Diastolic BP (mmHg)	77.6 (70.2–83.8)	78.7 (71.3–84.6)	76.9 (69.4–83.0)	0.16
Waist Circumference (cm)	86.7 (81.1–95.1)	89.8 (81.4–96.6)	89.3 (79.9–96.8)	0.13
Total Cholesterol (mg/dL)	187.2 (156.9–215.3)	189.5 (154.7–227.8)	196.1 (159.7–240.2)	0.041
HDL (mg/dL)	42.1 (34.5–53.6)	39.5 (32.9–51.8)	38.9 (31.4–50.5)	0.014
CRP	1.12 (0.51–2.29)	1.66 (0.74–3.53)	3.30 (1.50–8.34)	<.0001
< 1 mg/L	45%	34%	16%	<.0001
1–3 mg/L	38%	34%	31%	
3–10 mg/L	15%	28%	33%	
>10 mg/L	1.8%	3.2%	21%	
HIV-Related Factors				
HIV RNA (/1000 copies/ml)	0.4 (0.4–4.2)	0.4 (0.3–11.7)	0.6 (0.4–29.9)	0.008
Detectable HIVRNA	45%	51%	54%	0.12
Current CD4 count (cells/μL)	388 (244–575)	354 (225–558)	329 (156–514)	0.008
Detectable HCVRNA	23%	20%	20%	0.29
Injection drug use	23%	19%	21%	0.29
History of AIDS **	66%	70%	78%	0.18
HAART use (ever)	86%	88%	91%	0.50

* Statistics estimated using IPCW weights. Continuous data are represented as median (IQR).

** AIDS defined by CD4<200 or history of opportunistic infection or malignancy

TABLE 2
Association of Fibrinogen and CRP with 5-year mortality in HIV-infected participants*

Multivariable-Adjusted*					
OR (95% CI)					
	n	Unadjusted Death Rate	Fibrinogen**	CRP**	Fibrinogen + CRP***
Fibrinogen					
< 319 mg/dL	313	7.4%	reference	-	reference
319–406 mg/dL	306	9.7%	1.27 (0.72, 2.22) p=0.41	-	1.12 (0.63, 1.98) p=0.70
>406 mg/dL	303	24.7%	3.35 (1.99, 5.65) p<0.001	-	2.57 (1.46, 4.52) p=0.001
CRP					
< 1 mg/L	293	7.3%	-	reference	reference
1–3 mg/L	317	14.4%	-	2.34 (1.33, 4.11) p=0.003	2.08 (1.17, 3.70) p=0.013
>3 mg/L	312	19.3%	-	3.72 (2.09, 6.63) p<0.001	2.68 (1.46, 4.93) p=0.002

* OR, odds ratio; CI, confidence interval.

Multivariable-adjusted model controls for demographics, smoking, non-HDL cholesterol, hepatitis C virus infection, waist circumference, lean mass, CD4 count, and total duration of efavirenz, indinavir, and amprenavir

** Fibrinogen and CRP are shown entering the model individually.

*** Fibrinogen and CRP are shown entering the model jointly.

TABLE 3

Association of Fibrinogen and CRP with 5-year mortality in HIV-infected participants stratified by CD4 count

CD4 Category	n		Multivariable-Adjusted*		
			Fibrinogen**	CRP***	Fibrinogen + CRP***
			OR (95% CI)	OR (95% CI)	OR (95% CI)
CD4 < 200	213	Fibrinogen (per 100 mg/dL increase)	2.19 (1.83, 2.62) p<0.0001	-	1.93 (1.57, 2.37), p<0.0001
		CRP† (per doubling)	-	1.44 (1.29, 1.61) p<0.0001	1.25 (1.10, 1.42), p=0.001
CD4 200–350	231	Fibrinogen (per 100 mg/dL increase)	1.64 (1.35, 2.00) p<0.0001	-	1.43 (1.14, 1.79), p=0.002
		CRP (per doubling)	-	1.33 (1.19, 1.49) p<0.0001	1.16 (1.02, 1.32), p=0.022
CD4 > 350–500	189	Fibrinogen (per 100 mg/dL increase)	1.65 (1.34, 2.02) p<0.0001	-	1.43 (1.14, 1.81), p=0.002
		CRP (per doubling)	-	1.34 (1.20, 1.50) p<0.0001	1.17 (1.03, 1.33), p=0.017
CD4 > 500	289	Fibrinogen (per 100 mg/dL increase)	1.49 (1.22, 1.82) p<0.0001	-	1.30 (1.04, 1.63), p=0.022
		CRP (per doubling)	-	1.30 (1.16, 1.45) p<0.0001	1.13 (1.00, 1.29), p=0.055

* OR, odds ratio; CI, confidence interval. Multivariate-adjusted model controls for demographics, smoking, non-HDL cholesterol, hepatitis C virus infection, waist circumference, lean mass, CD4 count, and total duration of efavirenz, indinavir, and amprenavir.

** Fibrinogen and CRP are shown entering the model individually.

*** Fibrinogen and CRP are shown entering the model jointly.

† CRP is log2-transformed. Estimates are odds of death per doubling of CRP.