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Change in High-Sensitivity C-Reactive Protein Levels Following Initiation of Efavirenz-Based Antiretroviral Regimens in HIV-Infected Individuals

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Abstract

Elevations in C-reactive protein (CRP) are associated with increased cardiovascular disease (CVD) risk, increased HIV disease progression, and death in HIV-infected patients. Use of abacavir has been reported to increase CVD risk. We assessed the effect of virologically suppressive efavirenz (EFV)-based antiretroviral therapy on high sensitivity CRP (hsCRP) levels over a 96-week period with particular attention to the effect of gender and abacavir use. Banked sera from entry and week 96 visits of AIDS Clinical Trials Group A5095 participants were assayed for hsCRP, then analyzed by gender, abacavir randomization, and for correlation with changes in fasting metabolic parameters. Analyses of hsCRP were conducted in two phases and involved a total of 145 men and 51 women. hsCRP did not differ by gender at baseline but higher levels were seen at week 96 in women (median 6 mg/liter; Q1, Q3, 1.8, 13.8) compared to men (median 1.6 mg/liter; Q1, Q3, 0.9, 4.2, $p < 0.001$), with an estimated shift in hsCRP by gender of 2.5 mg/liter (95% CI 1.0, 5.1). There was no difference in hsCRP levels by abacavir use. Changes in hsCRP did not correlate with changes in insulin resistance or with changes in fasting lipids. Durably virologically suppressive therapy with EFV-based regimens did not decrease hsCRP levels over a 96-week period. hsCRP levels increased significantly only in women. Randomization to abacavir had no effect on changes in hsCRP levels. Changes in hsCRP levels did not correlate with changes in fasting metabolic parameters.

Introduction

An evolving body of work in the general population has linked elevated levels of C-reactive protein (CRP) with increased risk of future cardiovascular events.[1] In HIV-infected individuals, higher levels of CRP have been associated with HIV disease progression and with increased mortality in women.[2,3]

Few studies have examined changes in CRP levels following the initiation of antiretroviral (ARV) therapy. Possible gender differences were noted in a study of CRP following protease inhibitor (PI)-based therapy.[4] The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study group as well as a number of other groups have reported that the use of abacavir (ABC) as part of ARV therapy increases cardiovascular disease (CVD) risk[5–8]; however, this remains controversial, with other groups showing no increased risk.[9–11]

Utilizing banked sera from a completed study in ARV-naive subjects, the objectives of this study were to determine the effect of efavirenz (EFV)-based ARV therapy on high sensitivity CRP (hsCRP) levels over 96 weeks in subjects who responded optimally with durable suppression of their HIV RNA levels. We examined the influence of gender and the effect of randomized abacavir use on change in hsCRP levels and assessed the correlation of change in hsCRP to alterations

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in various fasting metabolic parameters obtained on the study participants.

Materials and Methods

This was a retrospective study of CRP levels in HIV-infected participants of the AIDS Clinical Trials Group (ACTG) A5095 clinical trial. A5095 was a U.S. multicenter, randomized, placebo-controlled, double-blind study designed to compare three nucleoside reverse transcriptase inhibitor (NRTI) ± nonnucleoside reverse transcriptase inhibitor (NNRTI)-containing ARV regimens for the initial treatment of HIV infection[12]: zidovudine (ZDV)/lamivudine (3TC)/ABC (coformulated) (Trizivir; GlaxoSmithKline), ZDV/3TC (coformulated) (Combivir; GlaxoSmithKline) plus efavirenz (EFV) (Sustiva; Bristol-Myers Squibb), and ZDV/3TC/ABC (coformulated) plus EFV. Week 0 and 96 sera collected, processed, and banked according to ACTG guidelines were forwarded and analyzed in batch at the ACTG Metabolic Lab (Quest Diagnostics). CRP levels were measured using the FDA-cleared, automated BN II *in vitro* diagnostic system (Dade Behring, Inc., Newark, DE). This hsCRP method uses a particle-enhanced immunonephelometric methodology with a sensitivity of 0.2 mg/liter. Subjects were selected if they were randomized to and remained on the original two EFV-containing groups (either ZDV/3TC/EFV or ZDV/3TC/ABC/EFV) through week 96 of the study and had documented HIV RNA <50 copies/ml at weeks 24 and 96 of the study.

The study was performed in two phases. The first phase had a sample size of 100 subjects and was designed to examine the correlation between hsCRP and changes in metabolic parameters following EFV-based ARV therapy and to assess gender differences. This original cohort targeted samples from subjects with sufficient stored samples who also met an additional criteria of availability of complete metabolic data as previously published at their week 0 and 96 visits.[13] The cohort design planned for equal numbers of men and women, but because of a limited number of women meeting the sampling requirements it included all women who met the sampling criteria and randomly selected males added to complete the study cohort of 100 subjects. Subsequently, in response to emerging data regarding potential CVD-related events associated with the use of abacavir, the second phase of this study was completed. This second new testing cohort enriched the original cohort by including all subjects who remained on their original EFV-containing regimen and had documented suppressed HIV RNA at week 24 and week 96 and had banked blood available for assay at weeks 0 and 96 (Fig. 1).

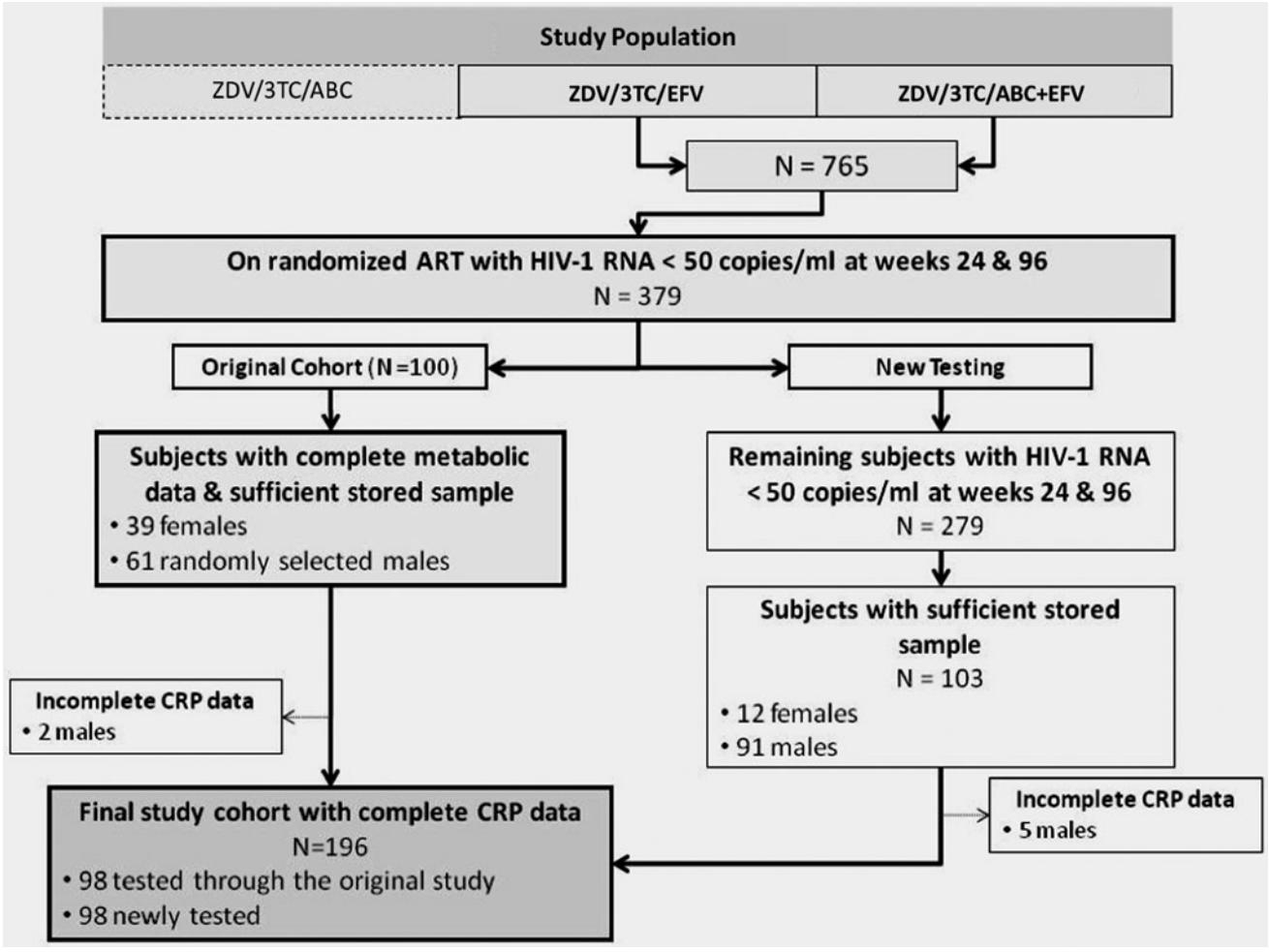

FIG. 1. Flow diagram of cohort selection.

Analyses of hsCRP with respect to gender and ABC randomization were conducted with data from all available subjects using a continuous scale as well as by classifications defined by the American Heart Association (AHA) grading scale[14] into low-risk, average-risk, high-risk, and outlier categories. Since full availability of metabolic data was guaranteed only in the original cohort, analyses of the hsCRP correlation to metabolic parameters were conducted only within this smaller original cohort.[13]

All analyses were performed as treated. Wilcoxon rank sum tests were conducted for the comparisons of continuous variables. Fisher's exact tests were conducted for the comparisons of categorical variables. The shift in hsCRP distribution between groups (week 0 measures, week 96 measures, and week 96 changes from baseline) and associated 95% confidence intervals were estimated using the Hodges–Lehmann method. Within-group changes in hsCRP from baseline to week 96 used two-sided sign tests; 95% confidence intervals were obtained by inverting the tests. The Jonckheere–Terpstra test was used to assess between-group differences in hsCRP risk category shifts over time. Spearman correlations were estimated between weeks 0 and 96 change in hsCRP and weeks 0 and 96 change in CD4 count and fasting metabolic measures [total, LDL- and HDL-cholesterol, triglycerides, lactate, insulin resistance (HOMA-IR), glucose]. All tests were conducted without adjusting the effect of other variables and the p-values were not adjusted for multiple comparisons. All statistical analysis used SAS version 9.1 (SAS Institute Inc., Cary, NC) and Proc StatXact (Cytel Software Corporation, Cambridge, MA).

Results

Cohort characteristics

A total of 379 subjects on the two EFV-containing arms of A5095 maintained long-term virologic suppression while on their initial randomized ARV regimen through 96 weeks of therapy. The original cohort of 100 subjects was comprised of all females meeting selection criteria ($n = 39$) and 61 randomly selected males. This cohort was enriched with an additional 103 subjects (12 females and 91 males) who remained on their originally assigned EFV-containing regimen with HIV RNA <50 copies/ml at weeks 24 and 96 and had sufficient stored sample. hsCRP data were incomplete for five male subjects (two in the original cohort and three from the new cohort), giving a final study population with complete hsCRP data of 196 subjects composed of 98 tested through the original cohort and 98 tested in the additional cohort (Fig. 1). Baseline characteristics of this analysis cohort by gender and by original, new, and overall categories are shown in Table 1. Original and newly studied cohorts were, in general, similar in characteristics except that the initial round of testing included more white, non-Hispanic women than Hispanic women. The baseline characteristics of all subjects with complete hsCRP data were in general similar to the A5095 subjects not included in the analysis population except for a slightly lower LDL-cholesterol [included in the analyses vs. not included in the analysis population (mean $\pm$ SD): 98 (34) mg/dl vs. 104 (31) mg/dl] (data not shown).

hsCRP change by gender

Median levels of hsCRP at week 0 and at week 96 by gender are shown graphically in Fig. 2A. hsCRP (mg/liter) did not differ at baseline between men and women [median (Q1, Q3): men 1.4 mg/liter (0.7, 3.9) versus women 2.3 mg/liter (0.9, 5.3); $p = 0.13$]. However, at 96 weeks, higher hsCRP levels were seen in women (median 6 mg/liter; Q1, Q3, 1.8, 13.8) compared to men (median 1.6 mg/liter; Q1, Q3, 0.9, 4.2; $p < 0.001$) with an estimated shift parameter by gender of 2.5 mg/liter (95% CI 1.0, 5.1). These differences were reflected

Table 1. Baseline Demographic and Metabolic Characteristics by Gender and by Original, New, and Combined (All) Cohorts

	Original men (N = 59)	*New men (N = 86)*	*Original women (N = 39)*	*New women (N = 12)*	*All men (N = 145)*	*All women (N = 51)*
Age at randomization (years), mean (SD)	39 (8)	36 (8)	40 (10)	41 (9)	37 (8)	40 (10)
Race/ethnicity						
White, non-Hispanic	24 (41%)	43 (50%)	18 (46%)	1 (8%)	67 (46%)	19 (37%)
Black, non-Hispanic	19 (32%)	25 (29%)	16 (41%)	5 (42%)	44 (30%)	21 (41%)
Hispanic	14 (24%)	15 (17%)	5 (13%)	6 (50%)	29 (20%)	11 (22%)
Other	2 (3%)	3 (3%)	0 (0%)	0 (0%)	5 (3%)	0 (0%)
Treatment arm						
ZDV/3TC/ABC/EFV	23 (39%)	45 (52%)	16 (41%)	6 (50%)	68 (47%)	22 (43%)
ZDV/3TC/EFV	36 (61%)	41 (48%)	23 (59%)	6 (50%)	77 (53%)	29 (57%)
IV drug use, previously	4 (7%)	9 (10%)	0 (0%)	1 (8%)	13 (9%)	1 (2%)
Hepatitis B antigen, positive	4 (7%)	3 (3%)	0 (0%)	0 (0%)	7 (5%)	0 (0%)
Hepatitis C antigen, positive	8 (14%)	7 (8%)	1 (3%)	2 (17%)	15 (10%)	3 (6%)
CD4 cell count (/mm^3), mean (SD)	250 (193)	230 (159)	200 (154)	249 (226)	238 (174)	211 (172)
HIV-1 RNA ($\log_{10}$ cp/ml), mean (SD)	5 (1)	5 (1)	5 (1)	5 (1)	5 (1)	5 (1)
Glucose (mg/dl), mean (SD)	91 (18)	87 (9)	85 (9)	106 (70)	89 (15)	88 (28)
Insulin (μlU/ml), mean (SD)	9 (6)	9 (6)	11 (8)	7 (2)	9 (6)	10 (7)
Total cholesterol (mg/dl), mean (SD)	162 (40)	148 (41)	165 (41)	156 (53)	155 (41)	164 (43)
HDL cholesterol (mg/dl), mean (SD)	32 (11)	34 (14)	35 (14)	33 (10)	33 (12)	35 (13)
LDL cholesterol (mg/dl), mean (SD)	102 (34)	91 (33)	101 (34)	97 (42)	96 (34)	101 (35)
Triglyceride (mg/dl), mean (SD)	163 (85)	143 (81)	139 (52)	122 (38)	153 (84)	136 (50)

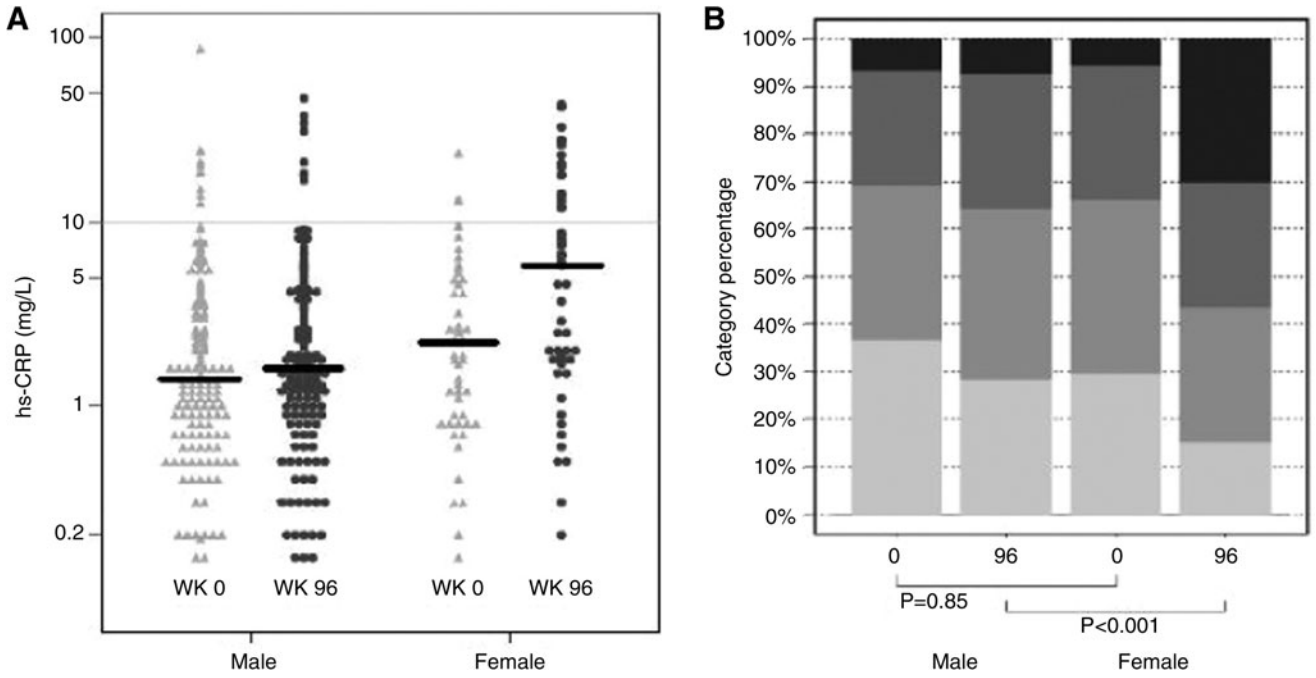

FIG. 2. Week 0 and week 96 hsCRP by gender. **(A)** Distribution by hsCRP (mg/liter) values. Black bars represent median values. **(B)** Distribution by American Heart Association Risk categories. From bottom to top: hsCRP <1 mg/liter (low risk), 1–3 mg/liter (average risk), >3–10 mg/liter (high risk), and >10 mg/liter (outlier).

in larger changes in hsCRP from baseline to week 96 in women (median 3.1 mg/liter; Q1, Q3, 0.2, 9.4) compared to men (median 0.1 mg/liter; Q1, Q3, −0.9, 1.4, $p < 0.001$) with an estimated shift in hsCRP by gender of 3.0 mg/liter (95% CI 1.4, 4.9). No correlations were seen among women between week 96 hsCRP change and change in body mass index (BMI) or in change in waist-to-hip ratio (WHR) [Spearman's correlation coefficients: BMI 0.22 (95% CI: −0.07, 0.51), $p = 0.24$; WHR −0.045, (95% CI: −0.35, 0.27), $p = 0.77$].

The AHA defines risk grade in hsCRP as <1 mg/liter (low risk), 1–3 mg/liter (average risk), >3–10 mg/liter (high risk), and >10 mg/liter (outlier; suggestive of other inflammatory processes). Week 0 and week 96 AHA hsCRP risk category by gender is shown in Fig. 2B. Again, values were not different by gender at baseline ($p = 0.85$) but were significantly different at 96 weeks ($p = 0.001$). The number of AHA hsCRP risk grade category shifts from baseline by gender is shown in Table 2 and shows a trend of greater proportion of shifts to a higher risk category for females compared to males ($p = 0.001$; Jonckheere–Terpstra test).

In assessing cardiovascular disease risk, the AHA recommends that hsCRP >10 mg/liter be discarded and repeated because extremely high hsCRP values may reflect other processes such as acute infection or other inflammatory processes.[14] Levels >10 mg/liter were found at week 0 in 10 (7%) men and 4 (8%) women and at week 96 in 8 (6%) men and 16 (31%) women. Analyses were repeated excluding subjects with hsCRP levels >10 mg/liter at either baseline or week 96. This led to the exclusion of 15 men (10% of the male cohort) and 16 women (31% of the female cohort). Although there remained evidence of a significant difference in week 0 to week 96 change between men and women, the magnitude of the difference was reduced [median change (Q1, Q3) in men of 0.1 mg/liter (–0.7, 1.2) vs. change in women of 0.8 mg/liter

Table 2. Number (%) of Subjects in American Heart Association hsCRP Risk Grade Categories at Week 96 by Gender and by Baseline Grade Categories

	Male				*Female*			
	Week 96 hsCRP risk grade				*Week 96 hsCRP risk grade*			
	Low: <1 mg/liter	*Average: 1–3 mg/liter*	*High: >3–10 mg/liter*	*Outlying: >10 mg/liter*	*Low: <1 mg/liter*	*Average: 1–3 mg/liter*	*High: >3–10 mg/liter*	*Outlying: >10 mg/liter*
Week 0 hsCRP risk grade								
Low: <1 mg/liter	21 (45%)	17 (36%)	9 (19%)	0 (0%)	4 (29%)	6 (43%)	2 (14%)	2 (14%)
Average: 1–3 mg/liter	14 (26%)	24 (45%)	14 (26%)	1 (2%)	1 (6%)	6 (33%)	a (44% J	3 (17%)
High: >3–10 mg/liter	3 (9%)	13 (37%)	15 (43%)	4 (11%)	2 (13%)	2 (13%)	4 (27%)	7 (47%)
Outlying: >10 mg/liter	0 (0%)	4 (40%)	3 (30%)	3 (30%)	0 (0%)	0 (0%)	0 (0%)	4 (100%)

(–0.2, 3.6), $p = 0.03$; estimated shift in hsCRP change by gender: 0.9 mg/liter (95% CI 0.1, 1.8)].

hsCRP change by treatment group

Median levels of hsCRP at week 0 and at week 96 by treatment group are presented graphically in Fig. 3. There were no differences in the distributions of hsCRP levels between the two randomization groups at baseline ($p = 0.95$) or at week 96 ($p = 0.38$) [baseline: 3TC/ZDV/EFV 1.5 mg/liter (0.9, 4.2) vs. ABC/3TC/ZDV/EFV 1.6 mg/liter (0.7, 4.4); week 96: 3TC/ZDV/EFV 1.9 mg/liter (0.9, 5.6) vs. ABC/3TC/ZDV/EFV: 2.0 mg/liter (1.2, 6.5)]. Correspondingly, there was no evidence of a difference in the distribution of change from baseline to week 96 by treatment groups [3TC/ZDV/EFV 0.3 mg/liter (–0.7, 2.9) vs. ABC/3TC/ZDV/EFV 0.4 mg/liter (–0.6, 3.3), $p = 0.75$]. No significant treatment differences were seen in distribution of risk grade at baseline ($p = 0.35$) or at week 96 ($p = 0.79$), or in week 0–96 change.

hsCRP change and change in metabolic parameters

As previously outlined, the original cohort of 100 subjects was selected based on the availability of a complete set of fasting metabolic parameters at baseline and week 96. Within this cohort, there were no significant correlations between weeks 0 and 96 changes in hsCRP and weeks 0 and 96 changes in BMI, CD4 count, or fasting metabolic measures [total, LDL- and HDL-cholesterol, triglycerides, lactate, insulin resistance (HOMA-IR), glucose] (Spearman's correlation coefficients were all within ± 0.1, with all $p > 0.3$).

Discussion

In this study, EFV-based ARV therapy in previously untreated HIV-infected individuals was associated with an increase in CRP levels over a 96-week period that was significant only in women and not in men. The inclusion of ABC in a base regimen of 3TC/ZDV/EFV did not result in an increase in hsCRP levels. Changes in CRP did not correlate with changes in any fasting metabolic blood parameter over 96 weeks.

The CRP in the systemic circulation is believed to act as the final end product of various converging inflammatory pathways that may reflect the cumulative effect of local vascular inflammation in predicting atherosclerosis risk.[15] The level of CRP predicts cardiovascular risk in the general population even among apparently healthy adults followed long-term over 8–10 years.[16–18] Its predictive value is independent of classic risk factors for coronary artery disease including the presence of diabetes, triglycerides, and BMI across all levels of the Framingham Risk Score.[16,18,19]

High rates of CRP have been reported in HIV-infected subjects[3,20] and recently the association between elevated CRP levels and increased myocardial infarction risk was shown specifically in HIV-infected subjects.[21] In that study, CRP and HIV independently increased the risk and the presence of both elevated CRP and HIV increased the odds of acute myocardial infarction to more than 4-fold compared with patients with neither elevated CRP nor HIV infection. High CRP levels of HIV-infected men in the Multicenter AIDS Cohort Study (MACS) were associated with HIV disease progression independent of CD4 lymphocyte counts and HIV RNA levels.[2] Regardless of progression to AIDS, this study found that HIV-infected individuals had a significant increase in CRP over time. CRP levels have been linked to a greater than 3-fold increased risk of death in HIV-infected women independent of age, BMI, CD4 count, and HIV RNA.[3] Similarly, in a resource-poor setting, high maternal CRP levels independently predicted HIV disease progression as well as maternal and child mortality.[22]

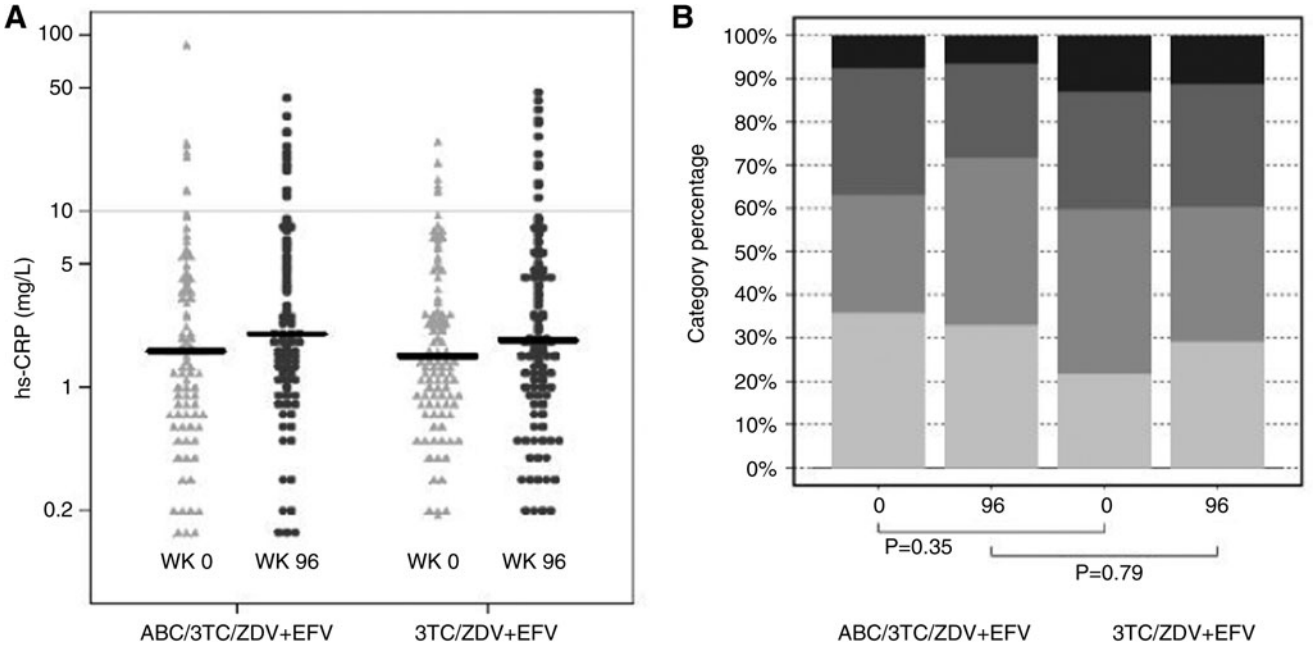

FIG. 3. Week 0 and Week 96 hsCRP by treatment groups. **(A)** Distribution by hsCRP (mg/liter) values. Black bars represent median values. **(B)** Distribution by American Heart Association Risk categories. From bottom to top: hsCRP <1 mg/liter (low risk), 1–3 mg/liter (average risk), >3–10 mg/liter (high risk), and >10 mg/liter (outlier).

Considering these associations, the impact of ARV therapy on CRP levels is of significant interest. Changes in CRP levels following PI therapy were studied in ACTG 5056s. This study assessed changes in CRP levels following indinavir-based HAART and noted that CRP levels remained stable or decreased slightly over an average of 42 months.[4] A similar slight decline overall was seen in the HEAT study over 96 weeks following initiation of lopinavir/ritonavir given with either ABC/3TC or tenofovir/emtricitabine.[23] The overall trend of decreasing CRP levels over time in both studies was observed only in men. Our study utilizing NNRTI-based HAART over 96 weeks found a slight nonstatistically significant increase in CRP in men. Whether this indicates that NNRTI-based regimens differ from PI-based therapy in altering CRP levels is unclear. CRP is mainly produced by hepatocytes in response to interleukin-6 (IL-6). As HAART can be expected to result in a substantial decrease in proinflammatory cytokines including IL-6, the failure of CRP to decrease following NNRTI-based HAART in our study is puzzling. However, other types of cells including adipocytes[24] and coronary artery smooth muscle cells[25] also produce CRP and production from these cells may account for the failure of CRP to decrease in our study. As CRP is also impacted by various other states and conditions such as genetic polymorphisms, dietary patterns, and many medical conditions that may not be inflammatory in nature, it is theoretically possible that the discrepancies between these studies were also due to such confounding conditions.[26]

A significant increase in hsCRP was seen only in women. This marked increase in hsCRP in women at week 96 resulted in 31% of women falling into the "outlier" category that the AHA recommends be discarded in the context of assessing cardiovascular disease risk in the general population. However, a later study assessing CRP across a full range of values found that levels >10 mg/liter may still be clinically useful for cardiovascular risk prediction.[18] Gender differences in hsCRP have been reported in the general population. Women with National Cholesterol Education Program (NCEP)-defined metabolic syndrome have higher hsCRP levels compared to men with the metabolic syndrome.[27] The use of oral contraceptives, particularly in overweight women, has been associated with significant rise in CRP.[28,29] Data on oral contraceptives were unfortunately not collected in A5095. At least two studies have cross-sectionally examined the differences in CRP levels specifically in HIV-infected women compared to HIV-seronegative controls. One study reported that CRP levels in HIV-infected women were comparable to that of HIV-seronegative controls.[20] Another study reported that CRP levels were higher in HIV-infected women and that the levels correlated with alterations in body composition, but not with HIV status.[30] The increase in CRP levels in women in our study is not likely to be due to changes in body composition as our study found no correlation between change in CRP levels and change in BMI or in WHR in women. Coinfection with hepatitis C has been reported to lower hsCRP levels,[20] but in our study the percent of subjects infected with hepatitis C was not markedly different.

CRP levels in the HIV population have been reported to correlate with traditional cardiovascular risk factors including LDL-cholesterol, HDL-cholesterol, cigarette smoking, increased BMI, and WHR.[30–32] Our study found no correlation between changes in hsCRP and changes in any metabolic parameters.

Some studies have suggested that ABC as part of ARV regimens is associated with an increased cardiovascular risk, with a risk that is particularly high with the recent initiation of ABC therapy.[5–8] Other studies have shown no increased risk.[9–11] We found that randomization to ABC in subjects previously naive to all ARV medications had no significant effect on changes in hsCRP levels over a 96-week period. This study presented the ideal situation to isolate the effect of ABC during first-time ARV therapy as the two treatment groups contained the same backbone of 3TC/ZDV/EFV and differed only in the random addition of ABC in one of the two groups. Early time points were not assessed in this study and it is possible that an early increase with subsequent decrease in hsCRP on ABC-containing therapy may have been missed.

The strengths of this study include the use of sera collected, processed, and banked under rigorous standardized criteria utilized by the ACTG, the availability of carefully obtained fasting metabolic parameters, and the ability to isolate the effect of ABC given in a randomized fashion within two treatment groups that otherwise utilized the same identical ARV medications. The limitations of this study include the lack of hsCRP data at very early time points or beyond 96 weeks following initiation of ART, the smaller percentage of women that comprised the cohort, and the lack of availability of certain data, such as hormonal contraceptive status, that may have helped to explain the higher CRP levels in women.

In summary, durably suppressive therapy with EFV-based regimens did not improve hsCRP levels over a 96-week period. Levels of hsCRP increased significantly in women. Randomization to ABC had no significant effect on changes in hsCRP levels. Changes in hsCRP levels did not correlate with change in insulin resistance or with changes in fasting lipids over the same time interval. In view of the significant increases in hsCRP seen in women in our study, further investigations to elucidate the causes and the implications of such an increase are warranted.

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Author Disclosure Statement

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References

1. Danesh J, Whincup P, Walker M, *et al.*: Low grade inflammation and coronary heart disease: Prospective study and updated meta-analyses. BMJ 2000;321(7255):199–204.

2. 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(1):64–70.
3. Feldman JG, Goldwasser P, Holman S, DeHovitz J, and Minkoff H: C-reactive protein is an independent predictor of mortality in women with HIV-1 infection. J Acquir Immune Defic Syndr 2003;32(2):210–214.
4. Henry K, Kitch D, Dube M, *et al.*: C-Reactive protein levels over time and cardiovascular risk in HIV-infected individuals suppressed on an indinavir-based regimen: AIDS Clinical Trials Group 5056s. AIDS 2004;18(18):2434–2437.
5. Sabin CA, Worm SW, Weber R, *et al.*: Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: A multi-cohort collaboration. Lancet 2008;371(9622): 1417–1426.
6. Worm SW, Sabin C, Weber R, *et al.*: Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. J Infect Dis Feb1 2010:201(3):318–330.
7. DAD Study Groups: Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. AIDS 2008;22(14):F17–24.
8. Cooper D, Bloch M, Humphries A, Amin J, Baker D, Emery S, and Carr A for the STEAL Study Investigators: Simplification with Fixed-dose Tenofovir/Emtricitabine or Abacavir/Lamivudine in Adults with Suppressed HIV Replication: The STEAL Study, a Randomized, Open-label, 96-Week, Non-inferiority Trial. 16th Conference on Retroviruses and Opportunistic Infections, Montreal, Canada, 2009. Abstract 576.
9. Brothers CH, Hernandez JE, Cutrell AG, *et al.*: Risk of myocardial infarction and abacavir therapy: No increased risk across 52 GlaxoSmithKline-sponsored clinical trials in adult subjects. J Acquir Immune Defic Syndr 2009;51(1): 20–28.
10. Lang S, Mary-Krause M, Cotte L, *et al.*: Impact of individual antiretroviral drugs on the risk of myocardial infarction in human immunodeficiency virus-infected patients: a case-control study nested within the French Hospital Database on HIV ANRS cohort C04. Arch Infern Med Jul 26 2010; 170(14):1228–1238.
11. Lichtenstein K, Buckner K, Armon C, Tedaldi E, Chmiel J, Wood K, *et al.*: Low CD4 Count is an Important Risk Factor for Cardiovascular Disease in the US HIV Outpatient Study (HOPS). 17th IAC 2008: Poster THPE0236, 2008.
12. Gulick RM, Ribaudo HJ, Shikuma CM, *et al.*: Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. N Engl J Med 2004;350(18):1850–1861.
13. Shikuma CM, Yang Y, Glesby MJ, Meyer WA, Tashima KT, Ribaudo HJ, Webb N, Bastow B, Kuritzkes DR, and Gulick RM for the AIDS Clinical Trials Group Protocol A5095 Study Team: Metabolic effects of protease inhibitor-sparing antiretroviral regimens given as initial treatment of HIV-1 infection (AIDS Clinical Trials Group Study—A5095). J Acquir Immune Defic Syndr 2007; 44(5): 540–550.
14. Pearson TA, Mensah GA, Alexander RW, *et al.*: Markers of inflammation and cardiovascular disease: Application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003;107(3):499–511.
15. Ikonomidis I, Stamatelopoulos K, Lekakis J, Vamvakou GD, and Kremastinos DT: Inflammatory and non-invasive vascular markers: The multimarker approach for risk stratification in coronary artery disease. Atherosclerosis 2008; 199(1):3–11.
16. 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(14):1387–1397.
17. Ridker PM, Cannon CP, Morrow D, *et al.*: C-reactive protein levels and outcomes after statin therapy. N Engl J Med. 2005; 352(1):20–28.
18. Ridker PM and Cook N: Clinical usefulness of very high and very low levels of C-reactive protein across the full range of Framingham Risk Scores. Circulation 2004;109(16):1955–1959.
19. Ridker PM, Buring JE, Cook NR, and Rifai N: C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: An 8-year follow-up of 14 719 initially healthy American women. Circulation 2003;107(3): 391–397.
20. 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(2):142–148.
21. Triant VA, Meigs JB, and Grinspoon SK: Association of C-reactive protein and HIV infection with acute myocardial infarction. J Acquir Immune Defic Syndr 2009;51(3):268–273.
22. Drain PK, Kupka R, Msamanga GI, Urassa W, Mugusi F, and Fawzi WW: C-reactive protein independently predicts HIV-related outcomes among women and children in a resource-poor setting. AIDS 2007;21(15):2067–2075.
23. McComsey GA Smith KY, Patel P, Bellos NC, Sloan L, Lackey P, Kumar PN, Sutherland-Phillips DH, Yau L, and Shaefer MS: Similar Reductions in Markers of Inflammation and Endothelial Activation after Initiation of Abacavir/Lamivudine (ABC/3TC) or Tenofovir/Emtricitabine (TDF/FTC) in the HEAT Study. 16th Conference on Retroviruses and Opportunistic Infections, Montreal, Canada, 2009.
24. Calabro P, Chang DW, Willerson JT, and Yeh ET: Release of C-reactive protein in response to inflammatory cytokines by human adipocytes: Linking obesity to vascular inflammation. J Am Coll Cardiol 2005;46(6):1112–1113.
25. Calabro P, Willerson JT, and Yeh ET: Inflammatory cytokines stimulated C-reactive protein production by human coronary artery smooth muscle cells. Circulation 2003;108(16): 1930–1932.
26. Kushner I, Rzewnicki D, and Samols D: What does minor elevation of C-reactive protein signify? Am J Med 2006; 119(2):166 e17–28.
27. Saltevo J, Vanhala M, Kautiainen H, Kumpusalo E, and Laakso M: Gender differences in C-reactive protein, interleukin-1 receptor antagonist and adiponectin levels in the metabolic syndrome: A population-based study. Diabet Med 2008;25(6):747–750.
28. Buchbinder S, Kratzsch J, Fiedler GM, *et al.:* Body weight and oral contraceptives are the most important modulators of serum CRP levels. Scand J Clin Lab Invest 2008;68(2):140–144.
29. Cauci S, Di Santolo M, Culhane JF, Stel G, Gonano F, and Guaschino S: Effects of third-generation oral contraceptives on high-sensitivity C-reactive protein and homocysteine in young women. Obstet Gynecol 2008;111(4):857–864.

30. Dolan SE, Hadigan C, Killilea KM, *et al.*: Increased cardiovascular disease risk indices in HIV-infected women. J Acquir Immune Defic Syndr. 2005;39(1):44–54.
31. Masia M, Bernal E, Padilla S, *et al.*: The role of C-reactive protein as a marker for cardiovascular risk associated with antiretroviral therapy in HIV-infected patients. Atherosclerosis 2007;195(1):167–171.
32. Boger MS, Shintani A, Redhage LA, *et al.*: Highly sensitive C-reactive protein, body mass index, and serum lipids in HIV-infected persons receiving antiretroviral therapy: A longitudinal study. J Acquir Immune Defic Syndr 2009;52(4):480–487.

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