



# 96 Week Effects of Suppressive Efavirenz-containing Antiretroviral Therapy, Abacavir, and Sex on hs-CRP in ACTG A5095

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## BACKGROUND

• C-reactive protein (CRP) is a circulating acute-phase reactant that is believed to be increased as part of an inflammatory response to tissue injury or infection.

• In the general population, CRP are predictive of future vascular events independent of traditional risk factors (1,2).

• CRP has been associated with HIV disease progression independent of CD4 and HIV RNA levels (3) and with increased mortality in HIV-infected women (4) as well as in other groups of HIV-infected individuals.

➢ Higher levels of hs-CRP as well as of IL-6 and D-dimer at study entry have been associated with an increased risk of all-cause mortality in the SMART study (5).

• On Indinavir-based HAART therapy, CRP levels were elevated at all time points assessed and tended to be stable or decrease over an average 42 month duration of follow-up (6).  
➢ In this ACTG study, possible gender effects were noted (unpublished data).

• We assessed the 96 week effect of NNRTI-based antiretroviral therapy on high sensitivity CRP (hs-CRP), and the effect of gender in the context of such therapy among ARV-naïve participants of the AIDS Clinical Trials Group A5095 (7) who were randomized to and demonstrated good virologic response in the original two efavirenz (EFV)-containing arms of this trial.

• Analysis of the effect on hs-CRP by arms [therapy with or without abacavir (ABC)] was subsequently added to the analyses performed.

## METHODS

• A5095 was a randomized, placebo-controlled, double-blind study designed to compare 3 NRTI +/- NNRTI containing ARV regimens for the initial treatment of HIV-1 infection (7):

➢ ABC/3TC/ZDV (coformulated) [Trizivir; GlaxoSmithKline]

➢ 3TC/ZDV (coformulated) [Combivir; GlaxoSmithKline] plus EFV [Sustiva; Bristol-Myers Squibb]

➢ ABC/3TC/ZDV (coformulated) plus EFV

• Week 0 and 96 sera from 100 patients were analyzed in batch at the ACTG Metabolic Lab (Quest Diagnostics) for hs-CRP levels

• Subjects were selected based on the following criteria:

➢ Randomized to and remaining on the original 2 EFV-containing arms (either 3TC/ZDV/EFV or ABC/3TC/ZDV/EFV) through week 96 of study

➢ Documented undetectable viral load (< 50 copies/ml) at study weeks 24 and 96

• Among 765 A5095 subjects randomized to the 2 EFV-containing arms, 385 met criteria for selection, and 169 of them had important metabolic measurements and sufficient sample volume available.

➢ The final sample size of 100 subjects included all available women (n=39) and a randomly selected group of 61 men from the 169 subjects.

• 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 hs-CRP distribution between two gender groups/ two treatment arms (week 0 measures, week 96 measures, and week 96 changes from baseline) and associated 95% confidence intervals were estimated using the Hodges-Lehmann method (Proc StatExact procedure in SAS).

• Two-sided sign tests were also conducted to evaluate the week 0-96 changes in hs-CRP between gender subgroups, with associated 95% confidence intervals obtained by inverting the tests.

• Correlations between week 96 change in hs-CRP from baseline and week 96 changes in CD4 and fasting metabolic measures were examined by Spearman's correlation coefficients.

## RESULTS

### Baseline Characteristics

**Table 1. Baseline characteristics**

• Baseline characteristics (including race, hepatitis status, CD4 count, HIV RNA and metabolic measures) did not differ statistically between the 100 selected subjects and the other 285 eligible subjects (p>0.5) with the exceptions of moderate differences in age (p=0.03), and the proportion of IVDU (p=0.04).

• Among the 100 selected subjects, there were no significant differences detected between men and women (p>0.05).

Characteristics		Subjects tested (N=100)			Other eligible subjects (N=285)
		Male (N=61)	Female (N=39)	All (N=100)	
Age at randomization (years)	Median (Q1, Q3)	40 (35, 45)	39 (32, 48)	40 (34, 46)	37 (31, 43)
Race/Ethnicity	White Non-Hispanic	25 (41.0%)	18 (46.2%)	43 (43.0%)	130 (45.6%)
	Black Non-Hispanic	20 (32.8%)	16 (41.0%)	36 (36.0%)	88 (30.9%)
	Hispanic	14 (23.0%)	5 (12.8%)	19 (19.0%)	60 (21.2%)
IV Drug Use	Ever	4 (6.6%)	0 (0.0%)	4 (4.0%)	32 (11.2%)
CD4 count(cells/mm <sup>3</sup> )	Median (Q1, Q3)	249 (77, 407)	195 (68, 266)	207 (73, 344)	245 (107, 363)
HIV-1 RNA (log10copies/mL)	Median (Q1, Q3)	4.8 (4.5, 5.5)	4.7 (4.2, 5.4)	4.8 (4.4, 5.4)	4.7 (4.4, 5.2)
Body Mass Index	Median (Q1, Q3)	25 (23, 28)	28 (23, 32)	26 (23, 29)	24 (22, 17)

Similar results were seen between the 100 selected subjects and the remaining 1047 A5095 study cohort except for age and IVDU (both p=0.02), and BMI [median (Q1, Q3): subjects tested 26 (23, 29) vs others 24 (22, 27), p=.09]

### hs-CRP Results Overall and by Gender

• Overall, a significant increase in hs-CRP was seen from week 0-96 (median change 1.3 mg/L 95% CI=[0.7, 2.7]), p<0.001.

• Wk 0 hs-CRP levels were not significantly different between women and men.

➢ median: 2.6 mg/L vs 1.6 mg/L, p-value=0.36.

➢ shift in the distribution: 0.3 mg/L; 95% CI: [-0.4, 1.3].

• At week 96, women had higher hs-CRP levels than men.

➢ median 6.6 mg/L vs 2.3 mg/L, p-value=0.001

➢ shift in the distribution: 3.0 mg/L; 95% CI: [0.9, 5.7]

• The differences reflected a larger increase in hs-CRP from baseline to week 96 for women than men.

➢ median 3.7 mg/L vs 0.5 mg/L, p-value=0.001

➢ shift in the distribution: 3.3 mg/L; 95% CI [1.3, 5.8]

• Subgroup analysis revealed that women had a significant change in hs-CRP from baseline to week 96 (median=3.7 mg/L, p-value<0.001, 95% CI of median = [1.7, 7.2]), which was not detected in men (median=0.5 mg/L, p-value 0.15, 95% CI = [-0.3, 1.3]).

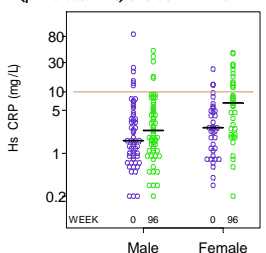
• In assessing cardiovascular disease risk, the American Heart Association (AHA) suggests that extremely high hs-CRP values may reflect other processes such as systemic inflammatory processes and recommends that an hs-CRP > 10 mg/L be discarded and repeated (8).

• Analyses were repeated excluding subjects with hs-CRP levels > 10 mg/L at either baseline or week 96 (n=21).

➢ Overall, week 0-96 hs-CRP levels continued to be significant (median change 1.1 mg/L, 95% CI [0.2, 1.7], p-value = 0.01).

➢ A similar trend in gender differences in wk 0-96 change was seen but no longer significant (median change in female 1.9 mg/L vs 0.5 mg/L in males, p-value=0.09).

**Figure 1. hs-CRP by gender at week 0 (pre-treatment) and at week 96**



## RESULTS continued

• The AHA defines risk grade in hs-CRP as < 1 mg/L (low risk), 1-3 mg/L (average risk) and > 3 mg/L (high risk). By these criteria - >33.3% of males compared to 53.8% of females demonstrated risk grade deterioration over 96 weeks, while 45.1% and 26.9% remained unchanged in grade and 21.6% and 19.2% demonstrated grade improvement respectively (p=0.20).

**Table 2. AHA hs-CRP risk grade by gender at week 0 (pre-treatment) and at week 96** (excludes the 21 individuals with hs-CRP >10 mg/L at baseline or week 96)

	Risk Grade	Overall (n=79)	Male (n=53)	Female (n=26)
Week 0	<1 mg/L (low)	23 (29.5%)	16 (30.8%)	7 (26.9%)
	1-3 mg/L (average)	33 (42.3%)	21 (40.4%)	12 (46.2%)
	>3-10 mg/L (high)	22 (28.2%)	15 (28.8%)	7 (26.9%)
Week 96	<1 mg/L (low)	17 (21.8%)	13 (25.0%)	4 (15.4%)
	1-3 mg/L (average)	28 (35.9%)	19 (36.5%)	9 (34.6%)
	>3-10 mg/L (high)	33 (42.3%)	20 (38.5%)	13 (50.0%)

### hs-CRP Results by Randomization Arm (with and without Abacavir)

• There was no difference between the 2 randomization arms with or without abacavir (3TC/ZDV/EFV vs ABC/3TC/ZDV/EFV) in baseline hs-CRP levels (shift in the distribution 0.5 mg/L with 95% CI = [-0.3, 1.7]) or in week 96 hs-CRP levels (shift in distribution 1 mg/L with 95% CI = [-0.3, 3.3]).

• The week 0-96 change in hs-CRP was not different between the arms (shift in the distribution 0.6 mg/L with 95% CI = [-1.5, 2.3]).

• Results remained unchanged when individuals with hs-CRP > 10 mg/L were excluded from analyses. No significant treatment differences were seen in distribution of risk grade at baseline or at week 96, or in week 0-96 change.

**Table 3. hs-CRP (median [CI]) by randomization arms**

	Total (N = 100)	ZDV/3TC/ABC/EFV (n=39)	ZDV/3TC/EFV (n=61)	P-value
Week 0	2.3 (0.9, 4.9)	3.2 (1.0, 5.8)	2.0 (0.9, 4.4)	0.247
Week 96	3.6 (1.5, 8.1)	5.2 (1.8, 9.0)	3.0 (1.3, 7.5)	0.107
Week 0-96 change	1.3 (-0.4, 4.5)	1.7 (0.1, 5.3)	1.1 (-0.5, 4.3)	0.500

### Correlations among Week 0-96 Change in hs-CRP and Other Variables

There was no significant correlations between the week 0-96 change in hs-CRP and week 0-96 change in body mass index, CD4 count or fasting metabolic measures [Total, LDL and HDL-cholesterol, triglycerides, lactate, insulin resistance (HOMA-IR), glucose] (Spearman's correlation coefficients all within +/- 0.1, with all p-values ≥ 0.3).

## CONCLUSIONS AND DISCUSSIONS

• Durably suppressive therapy with EFV-based regimens did not improve hs-CRP levels over a 96-wk period.

• hs-CRP levels increased significantly in women but not men over this interval; the sensitivity analyses which excluded subjects with hs-CRP levels > 10 mg/L, however, showed less significant evidence on the increase (P=0.094).

• Randomization to ABC had no significant effect on changes in hs-CRP levels.

• The limitation of this study is the small sample size (N=100) and the potential bias introduced by the sample selection.

### References:

1. Stoneh J, Whincup P, Walker M, et al.: Low grade inflammation and coronary heart disease: prospective study and updated meta-analysis. *BMJ* 2000; 321(7255): 199-204.
2. Ricker PK, Buring JE, Cook NR, Rifkin 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): 391-7.
3. Liu S, Sharifi AR, Kingley LA, et al.: C-reactive protein is a marker for human immunodeficiency virus disease progression. *Aids* 2004; 18(4): 44-70.
4. Feldman JJ, Goldwasser P, Holman S, DeWalt J, 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): 210-4.
5. Kuter LJ, Tracy R, Behrooz W, De Wit S, et al for the INSIGHT SMART Study Group: Plasma Med. 2008 October; S100: e203.
6. Henry K, Kibou 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 505As AIDS*. 2004;18(18):2434-7.
7. Gulick RM, Ribaudo H, 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):1850-61.
8. Pearson TA, Merz H, 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(21): 499-511.

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