Poster 732

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

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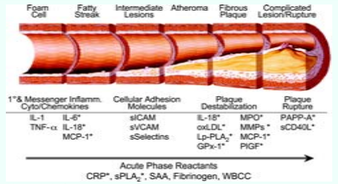
Introduction

- Endothelial dysfunction and chronic inflammation have been reported in HIV-1 infected patients.[1]
  - Elevations in the endothelial marker, sVCAM-1, were observed during treatment interruption in STACCATO[2]
  - Elevations in IL-6 and hsCRP were proposed by SMART investigators as a possible biologic mechanism for the increased risk of cardiovascular (CV) events among patients treated with ABC in the SMART study[3]
- This analysis compared the effects of initiating ABC/3TC and TDF/FTC on three inflammatory biomarkers in a prospective, randomized study of ART-naïve patients.

CV Risk and Role of Biomarkers

- Cardiovascular disease is the leading cause of death in the general population. Death due to non-AIDS defining illnesses is becoming increasingly more common in HIV-infected patients.[1]
- HIV infection may increase CV risk in part through uncontrolled viral replication leading to dyslipidemia, endothelial dysfunction, and elevation of pro-inflammatory markers.
- HIV-infected individuals have a greater prevalence of smoking, insulin resistance and lipid abnormalities compared to those uninfected.
- Pro-inflammatory markers have been used as markers for increased CV risk.

Figure 1. Pathogenesis of Atherosclerosis



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- Development of atherosclerosis is a complex process mediated by many inflammatory markers including:
  - hsCRP (High Sensitivity C-Reactive Protein): acute phase protein which is an independent risk factor for predicting CV disease (CVD)
    - Factors increasing hsCRP: elevated BP, elevated BMI, smoking, metabolic syndrome, diabetes, low HDL, high TG, estrogen/progesterone use, chronic infection or inflammation
  - IL-6 (Interleukin-6): procoagulant cytokine that stimulates the inflammatory cascade through effects on hsCRP and macrophages and is also an independent predictor of CVD.
  - sVCAM-1 (Soluble vascular cell adhesion molecule-1): activated by cytokines from the surface of endothelial cells and leukocytes early in the atherosclerotic process and is a marker of endothelial activation and local or systemic inflammation.

Methods

- Available stored paired plasma samples from HEAT study subjects were retrospectively analyzed for hsCRP, IL-6, and sVCAM-1 concentrations at baseline (BL), week 48, and week 96.
  - HEAT was a large, randomized, double-blind, placebo-matched, 96 week study that previously demonstrated the non-inferiority of ABC/3TC compared to TDF/FTC at week 48, each in combination with LPV/r in 688 ART-naïve subjects.
- Biomarker concentrations were analyzed by Quest Diagnostics using fixed rate nephelometry for hsCRP and ELISA for both IL-6 and sVCAM-1.
- Concentration data from paired samples were evaluated using geometric mean (GM) concentrations and percent change from baseline in GM (95%CI).

Results

- 476/688 (69%) subjects had paired concentration data (BL & wk 48 or BL & wk 96) for analysis. Among these 476 subjects, 22 (16 ABC/3TC; 6 TDF/FTC) had confirmed virologic failure.
- Baseline characteristics were similar between the biomarker and overall HEAT study population.
- Baseline medical conditions were generally comparable between groups (ABC/3TC vs. TDF/FTC) with the exception of the following:
  - myocardial infarction - none vs. 1 subject on TDF/FTC
  - hypercholesterolemia – 33 (14%) vs. 22 (9%) subjects
  - diabetes mellitus – 6 (2%) vs. 11 (5%) subjects
- Using an expanded definition of CVD, 6 subjects had CV-related events during study; all had pre-existing medical conditions or contributing risk factors and all were judged by investigators as non-drug related:
  - 2 with ABC/3TC: chest pain (negative stress test), TIA*
  - 4 with TDF/FTC: exacerbation of CHF, cardiac arrest from cocaine overdose, CVA*, TIA*

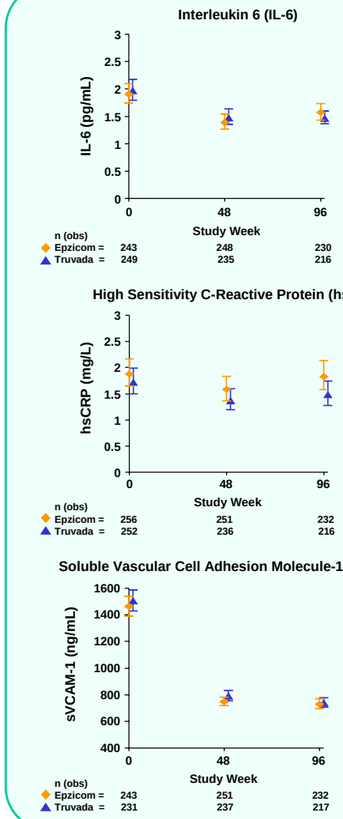
  * Events included as part of expanded CVD definition
- 14 subjects were *HLA-B*5701* positive (8 ABC/3TC; 6 TDF/FTC) and 13 also had biomarker data (7 ABC/3TC; 6 TDF/FTC) on retrospective analysis; 6/7 subjects on ABC reported a suspected ABC hypersensitivity.
  - There was one subject positive for *HLA-B*5701* who tolerated ABC for 96 weeks; biomarkers remained stable or declined similar to the overall study population.

Table 1. Baseline Demographics and Characteristics of Biomarker Population

		ABC/3TC n = 243	TDF/FTC n = 233
Mean Age, yrs (range)		39 (20-64)	39 (18-65)
Female sex		13%	16%
Race	**White**	55%	55%
	African-American	32%	29%
	Other*	13%	16%
Hispanic/Latino Ethnicity		21%	20%
Median Plasma HIV-1 RNA, log_{10} c/mL		4.89	4.87
	HIV-1 RNA ≥100,000 c/mL	45%	40%
Median CD4+ count (cells/mm³)		224	201
	<50 cells/mm³	16%	18%
	50-<200 cells/mm³	27%	32%
	≥ 200 cells/mm³	56%	51%
CDC Class C		14%	17%
Hepatitis B		3%	3%
Hepatitis C		6%	5%
hsCRP CV Risk Categories			
	<1 mg/L (low risk)	29%	34%
	1-3 mg/L (average risk)	37%	32%
	>3-10 mg/L (high risk)	27%	28%
	>10 mg/L (non-cardiac)	7%	6%

Notable difference (> 5%) in African American race in the TDF/FTC arm: overall HEAT population 36% vs.subset with biomarker data 29%.
*Other includes American Indian, Asian, Arabic/North African, mixed race and other race.

Figure 2. Biomarker Concentrations by Study Week, Geometric Mean (GM) [95% CI]



- hs-CRP levels increased in women from a GM of 1.61 mg/L (95% CI: 1.25, 2.08) at baseline to a GM of 2.24 mg/L at 96 weeks (95% CI: 1.68, 3.00); these increases were not seen in men and were independent of treatment (GMs 2.26, 2.23 for ABC/3TC, TDF/FTC respectively at 96 weeks).

Figure 3. Percent Change in Biomarker Concentrations

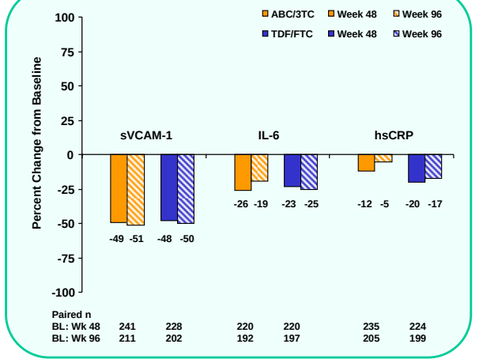
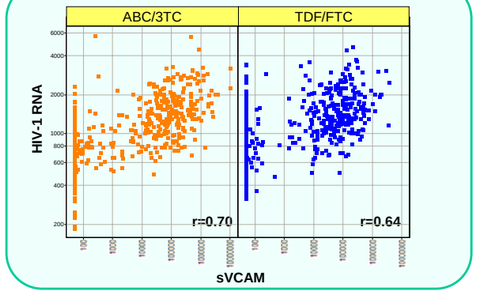


Figure 4. Correlation of sVCAM-1 and HIV-1 RNA (Week 96)



- Declines from baseline in sVCAM-1, IL-6, and hsCRP concentrations were observed at weeks 48 and 96 in both groups; there was no difference in the degree of reduction between arms for any of the 3 biomarkers (p>0.05).
- Level of HIV-1 RNA was correlated with sVCAM-1 concentrations across all timepoints (Figure 4).
- A pilot exploration of week 24 biomarker concentrations limited to those subjects with matched baseline demographics and LDL categories in the two treatment arms resulted in too few subjects for meaningful analysis.

Table 2. Change in hsCRP Category at Week 96

Change in hsCRP category at Week 96*	ABC/3TC n = 205	TDF/FTC n = 199
No shift from baseline	42%	46%
Upward shift from baseline (higher CV risk)	28%	23%
Downward shift from baseline (lower CV risk)	30%	31%

* Refer to Table 1 for hsCRP categories of CV risk

- Shifts in CV risk as measured by changes in hsCRP categories were similar between treatment groups at week 96.

Discussion

- Traditional CVD risk factors such as age, male sex, hypertension, hypercholesterolemia, low high-density lipoprotein cholesterol, smoking, and diabetes mellitus are common in HIV and are strongly associated with increased CV risk.
- Novel biomarkers have been suggested as indicators of increased cardiovascular risk and may provide additional information over and above the use of traditional risk factors in both general and HIV populations.
- Comparable declines in circulating sVCAM-1, IL-6, and hsCRP were observed in both groups suggesting a similar decrease in inflammation with both antiretroviral therapies. There were no significant differences between groups for all biomarkers evaluated.
- Most subjects had low to average CV risk as measured by hsCRP levels at baseline and the majority had a decrease or no change in hsCRP levels on therapy.
- Few CV-related events occurred during study, thus a correlation between inflammatory markers and nucleoside backbone with CV risk was not possible. The net decrease in inflammatory markers observed differs from the SMART study for ABC.
- As demonstrated in previous studies, lack of virologic response is significantly correlated with no change or slight increase in sVCAM-1 levels mirroring observations in patients off treatment.

Conclusions

- ABC/3TC and TDF/FTC containing therapy similarly decreased inflammatory markers associated with CV risk in antiretroviral-naïve patients.
- Few CV events occurred in HEAT and event rate was similar between arms.
- The declines in hsCRP, IL-6, and sVCAM-1 concentrations in the HEAT study do not support the hypothesis of an ABC-induced inflammatory response leading to increased CV risk.

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Acknowledgements

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