



# The Effect of Hepatitis C Infection on Metabolic Parameters following Initial Therapy of HIV Infected Subjects with Nucleoside +/- NNRTI Regimens

Cecilia M Shikuma<sup>\*1</sup>, Heather J Ribado<sup>2</sup>, Marshall J Glesby<sup>3</sup>, William A Meyer<sup>4</sup>, Karen T Tashima<sup>5</sup>, Barbara Bastow<sup>6</sup>, Daniel R Kuritzkes<sup>7</sup>, Roy M Gulick<sup>3</sup>, and AIDS Clinical Trials Group A5095 Study Team <sup>1</sup> University of Hawaii, Honolulu, HI; <sup>2</sup> Harvard School of Public Health, Boston, MA; <sup>3</sup> Weill Medical College of Cornell University, New York, NY; <sup>4</sup> Quest Diagnostics, Baltimore, MD; <sup>5</sup> Brown University, Providence, RI; <sup>6</sup> Social & Scientific Systems Inc., Silver Spring, MD; <sup>7</sup> Brigham and Women's Hospital, Boston, MA

Cecilia M. Shikuma M.D.  
Hawaii AIDS Clinical Research Program  
Leahi Hospital  
3075 Kilauea Ave. Young Blvd  
5th Fl  
Honolulu, HI 96816  
Email: [shikuma@hawaii.edu](mailto:shikuma@hawaii.edu)  
Ph: (808) 737-2751  
Fax: (808) 735-7047

## ABSTRACT

**Background:** Limited information is available on the impact of hepatitis C (HCV) co-infection on metabolic changes in HIV subjects starting initial nucleoside +/- non-nucleoside reverse transcriptase inhibitor (NNRTI) antiretroviral (ARV) therapy. We assessed fasting metabolic parameters in subjects with and without HCV antibody following initiation of such therapy in an AIDS Clinical Trials Group clinical trial.

**Methods:** Analyses involved 78 HCV-antibody positive (HCV+) and 760 HCV-antibody negative (HCV-) subjects in A5095, a study of initial treatment of HIV infection with a triple-nucleoside (ZDV/3TC/ABC), 3-drug efavirenz (EFV) (ZDV/3TC+EFV), or 4-drug EFV (ZDV/3TC/ABC+EFV) regimen. Fasting metabolic parameters [total, HDL and LDL cholesterol (C), lactate, triglyceride (TG), glucose, and insulin with calculation of HOMA-IR] were assessed at week 0, 24, and 96. The distribution of metabolic parameters at each week and their changes from baseline (week 0-24 and week 0-96) were compared by Wilcoxon test between HCV+ and HCV- subjects.

**Results:** At baseline, all metabolic parameters were similar except for slightly higher TG in HCV+ subjects [HCV+ vs HCV-(median): 135 vs 122 mg/dL, p=0.04]. Numbers of HCV+ subjects were equal across arms. Following therapy, HOMA-IR levels were modestly higher and LDL-C levels were modestly lower in the HCV+ compared to HCV- subjects at both week 24 [HCV+ vs HCV- (median): HOMA-IR 2.41 vs 1.92, p=0.03; LDL-C (mg/dL) 95 vs 108, p=0.002] and week 96 [HCV+ vs HCV-(median): HOMA-IR 2.89 vs 2.16, p=0.017; LDL-C (mg/dL) 98 vs 113, p=0.012]. Rates of diabetes (fasting glucose  $\geq$  126 mg/dL) were similar at baseline; however at week 96, a greater proportion of HCV+ compared to HCV- subjects had diabetes (9% vs 3%, p=0.03). While differences were modest, changes from week 0-24 showed greater increases in HDL-C and in HOMA-IR and smaller increases in LDL-C and TG in HCV+ compared to HCV- subjects (all p < 0.05); similar trends were apparent in the week 0-96 changes but only HDL-C remained statistically significant (p=0.02). No differences in lactates were found either in distribution at the assessed timepoints or in change over time.

**Conclusions:** HCV co-infection modestly alters some metabolic parameters following NRTI +/- NNRTI ARV treatment. In particular, HCV co-infection results in higher insulin resistance and rates of diabetes, and lower LDL-C values. The cardiovascular impact of these differences remains to be determined.

## BACKGROUND

HIV/hepatitis C (HCV) co-infected individuals on highly active antiretroviral therapy (HAART) have been reported to have lower total and LDL cholesterol values than HIV mono-infected individuals [1-3]. Higher rates of diabetes, hyperglycemia and insulin resistance have also been reported in co-infected individuals [1, 4-6]. The specific role of antiretroviral regimens in the development of these differences as HIV/HCV co-infected individuals are placed on 1st time HAART have been less studied, particularly in PI-sparing regimens.

## METHODS

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

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

The triple-nucleoside arm (ZDV/3TC/ABC) of ACTG study A5095 was discontinued early because of virologic inferiority following recommendation by the study's Data and Safety Monitoring Board. Some subjects on this arm enrolled into an amended study randomizing subjects to the addition of EFV or tenofovir (TDF) to the original triple-nucleoside regimen.

## METHODS continued

\*This intent-to-treat metabolic analyses included all 1052 subjects of all arms from A5095 who had an evaluable hepatitis C (HCV) antibody test. Subjects without an HCV test or with results that were indeterminate were excluded (n=95). Missing data were ignored and no adjustments were made for treatment arms or lipid lowering agents. Fasting metabolic measures were compared between HCV antibody positive and HCV antibody negative subjects at week 0, week 24, and week 96. The absolute change from baseline to week 24 and to week 96 for each parameter were also assessed. Metabolic measures assessed were:

- Total, LDL and HDL Cholesterol
- Triglycerides
- Glucose and HOMA-IR
- Lactate

\*Fasting was defined as nothing by mouth except water and medications for a minimum of 8 hours before the blood draw. \*Wilcoxon tests for continuous variables and Fisher's exact test for categorical variables were used to compare differences between HCV+ and HCV- groups at weeks 0, 24 and 96 and changes from weeks 0-24 and from weeks 0-96. No adjustments were made for multiple comparisons; marginally significant p-values should be considered cautiously.

## RESULTS

### A5095 Baseline Characteristics of Cohort

Numbers of HCV+ subjects were equally distributed across the A5095 arms. Differences between HCV+ and HCV- groups were detected in age and IV drug history (p<0.001).

	Overall (N=1052)	HCV positive (n=108)	HCV negative (n=944)
Age (Year)	Median	38	42
Race/Ethnicity (%)			
		433 (41%)	34 (3%)
		379 (36%)	50 (46%)
		216 (21%)	193 (20%)
Gender (%)			
		848 (81%)	84 (78%)
		209	211
		4.8	4.8
IV drug history (%)			
		110 (10%)	60 (56%)
			51 (5%)

### A5095 Metabolic Parameters in HCV+ vs HCV- Subjects at Weeks 0, 24 and 96

Lower levels of LDL Cholesterol and higher levels of HOMA-IR were noted in the HCV+ group compared to the HCV- group at both week 24 and week 96.

	WEEK 0		P-Value	WEEK 24		P-Value	WEEK 96		P-Value
	HCV+	HCV-		HCV+	HCV-		HCV+	HCV-	
Approximate N available for assay*	72	731		73	676		50	497	
Total Cholesterol [median (Q1, Q3)] (mg/dL)	157 (136,177)	156 (136,179)	0.96	173 (147,194)	177 (153, 205)	0.16	177 (145, 202)	188 (163, 217)	0.05
LDL Cholesterol [median (Q1, Q3)] (mg/dL)	93 (73, 116)	99 (79, 118)	0.23	95 (76, 125)	108 (89, 130)	0.002	98 (80, 128)	113 (92, 137)	0.01
HDL Cholesterol [median (Q1, Q3)] (mg/dL)	32 (25, 39)	33 (26, 40)	0.29	45 (37, 56)	41 (33, 50)	0.02	46 (34, 51)	42 (34, 51)	0.51
Triglycerides [median (Q1, Q3)] (mg/dL)	135 (110, 180)	122 (89, 174)	0.04	122 (94, 183)	132 (92, 195)	0.74	146 (112, 183)	150 (100, 236)	0.99
Glucose [median (Q1, Q3)] (mg/dL)	87 (81, 91)	86 (81,92)	0.82	92 (87, 100)	92 (87, 98)	0.59	92 (86, 104)	93 (88, 101)	0.95
HOMA-IR [median (Q1, Q3)]	1.8 (1.1, 2.6)	1.7 (0.1, 1.0)	0.58	2.4 (1.6, 3.6)	1.9 (1.3, 3.0)	0.03	2.9 (1.8, 5.0)	2.2 (1.4, 3.6)	0.02
Lactate [median (Q1, Q3)] (mg/dL)	8 (6, 10)	8 (6, 10)	0.97	9 (7, 11)	9 (7, 13)	0.16	11 (7, 13)	10 (7, 13)	0.35

Gray cells indicate p<0.05. \*Available sample numbers differed marginally across assays.

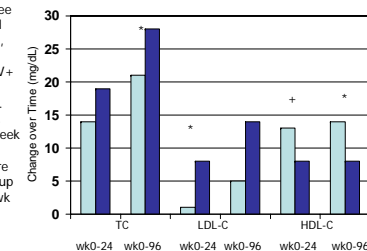
## RESULTS continued

### A5095 Change in Cholesterol and Triglyceride Parameters in HCV+ vs HCV- Subjects over Weeks 0-24 and over Weeks 0-96

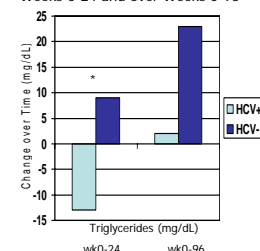
Some modest but statistically significant differences in the degree of change in some lipid parameters (TC, LDL-C, HDL-C, and TG) were noted between the HCV+ and HCV- groups

[\*p<0.05; +p=0.001]. Most of the differences were noted between week 0 and 24. Greater increases in HDL-C were noted in the HCV+ group for both wk 0-24 and wk 0-96 changes.

Changes in Cholesterol values over Weeks 0-24 and over Weeks 0-96

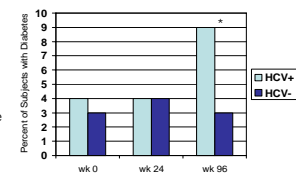


Changes in Triglycerides over Weeks 0-24 and over Weeks 0-96



### Rates of Diabetes (fasting Blood Glucose > 126 mg/dL) and Changes in Fasting Glucose and HOMA-IR in HCV+ vs HCV- Subjects

As shown in Table to right, rates of diabetes (fasting blood glucose > 126 mg/dL) were similar at baseline and at week 24. However at week 96, a greater proportion of HCV+ compared to HCV- subjects had diabetes (\* p=0.03). Relative risk for incidence of diabetes in HCV+ vs HCV- (unadjusted for other variables); wk 24 [RR 1.05, 95% CI 0.3, 3.5, p=0.94], wk 96 [RR 3.49, 95% CI 1.4, 8.6, p=0.01].



No differences between HCV+ and HCV- groups were noted in change in plasma glucose levels between wk 0-24 or between wk 0-96. However, there was some evidence of a higher increase in log[HOMA IR] in the HCV+ group in the wk 0-24 assessment (p=0.02).

## CONCLUSIONS

HCV co-infection modestly alters some metabolic parameters following NRTI +/- NNRTI ARV treatment. In particular, compared to HIV mono-infected individuals, NRTI+/- NNRTI ARV treatment in HCV/HIV co-infected individuals results in:

- Higher insulin resistance and rates of diabetes
- Lower levels of LDL-C values
- Higher increases in HDL-C values

The cardiovascular impact of these differences remains to be determined.

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