Poster #917
Abstract #S-134

Biomarkers of Vascular Dysfunction in HIV-Infected Children With and Without Hyperlipidemia

Tracie Miller[1], Denise Jacobson[2], Armando Mendez[1], Rohan Hazra[3], Mitchell Geffner[4], George Siberry[3], William Borkowsky[5], Kunjal Patel[2], Elizabeth McFarland[6], and Russell Van Dyke[7] for the Pediatric HIV/AIDS Cohort Study (PHACS)

[1]University of Miami Miller School of Medicine, Miami FL; [2]Harvard School of Public Health, Boston MA; [3]The Eunice Kennedy Shriver National Institute of Child Health and Human Development; [4] Saban Research Institute of Childrens Hospital Los Angeles, University of Southern California, Los Angeles CA; [5]New York University School of Medicine, New York NY; [6]Children's Hospital of Denver, University of Colorado Health Sciences, Denver CO; [7]Tulane University, New Orleans LA

Tracie L. Miller, MD
University of Miami
Dept of Pediatrics
PO Box 016820
Miami FL 33101
Tel: 305-243-1423
Fax: 305-243-8475
tracie.miller@miami.edu

ABSTRACT*

Background: Limited information exists regarding metabolic cardiovascular (CV) risk among HIV-infected (HIV+) children. We compared biomarkers of vascular dysfunction among perinatally infected HIV+ children with and without hyperlipidemia (HL) and HIV-uninfected (HIV-) children.

Methods: HIV+ children enrolled in the PHACS Adolescent Master Protocol (AMP) study have fasting lipid profiles and clinical outcomes (CD4 %, HIV viral load (VL), antiretroviral therapies and anthropometrics) evaluated annually. Based on lipid profiles, HL was defined as > 1 of the following: total cholesterol (CHOL) > 200 mg/dL; LDL CHOL > 130 mg/dL; triglycerides > 110 mg/dl in children < 10 y or > 150 mg/dL for 10-19 y; or HDL cholesterol < 35 mg/dL. The first 50 HIV+ with HL (Group A) and without HL (Group B) were compared to 55 HIV- controls (Group C). Biomarkers of vascular dysfunction (CRP, IL-6, MCP-1, PAI-1, fibrinogen, P-selectin, I-CAM-1, V-CAM-1, E-selectin and adiponectin) were measured in all groups. The groups were compared using Kruskal Wallis test for continuous variables and exact test for nominal variables. A p value < 0.01 was considered statistically significant because the groups were compared on many outcomes.

Results: Overall prevalence of HL (measured in mg/dl) in the HIV+ AMP cohort was 45% (117/262). Groups were similar on age (12 y), sex (50% male), race (62%-76% Black, non-Hispanic) and BMI (61% with BMI Z-score between -1.0 and 1.0). Group A (vs Group B) had significantly higher CHOL (mean 205 [IQR 176, 220] vs 158 [IQR 141, 179]), LDL CHOL (mean 128 [IQR 92, 147] vs 87 [IQR 74, 107]), and triglyceride (mean 151 [IQR 96, 185] vs 84 [IQR 53, 118]). There were no differences in CD4%, VL, or HDL CHOL. A greater number of children with HL were on PI compared to those without (90% vs 70% p=0.02). Biomarkers of vascular dysfunction were compared across groups (Table). HIV groups (A and B) differed from controls on several biomarkers yet these measures were similar among HIV-infected children with and without HL.

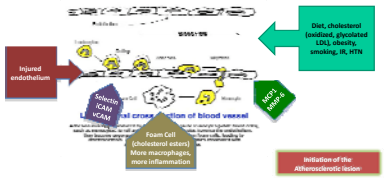
Conclusion: HIV+ children with and without HL show greater levels of biomarkers than controls. These changes may reflect vascular dysfunction and may be associated with elevated CV risk over the long-term. Differences are pronounced in coagulant and endothelial dysfunction.

	Group A (n=50) HIV+ HL	Group B (n=50) HIV+ w/o HL	Group C (n=55) HIV-	P-Value*
Inflammation				
CRP	0.35 (0.2, 0.75)	0.40 (0.2, 1.1)	0.20 (0.1, 0.6)	0.13
IL-6	0.95 (0.6, 1.5)	0.9 (0.6, 1.3)	0.8 (0.4, 1.3)	0.19
MCP-1	122 (97, 161)[1]	104 (84, 141)	103 (90, 123)[1]	0.06
Coagulant dysfunction				
Fibrinogen	399 (361, 451)[1]	375 (328, 424)[2]	334 (282, 377)[1, 2]	<0.001
P-selectin	38.5 (30.7, 50.5)[1]	36.3 (27.3, 55.1)[2]	28.6 (22.3, 35.7)[1, 2]	<0.001
Endothelial dysfunction				
I-CAM-1	303 (237, 381)[1]	286 (244, 352)[2]	231 (162, 253)[1, 2]	<0.001
V-CAM-1	757 (645, 948)[1]	757 (642, 933)	682 (578, 841)[1]	0.07
E-selectin	51.8 (42.2, 72.0)[1]	45.9 (33.0, 62.4)[2]	24.9 (20.6, 34.4)[1, 2]	<0.001
Metabolic dysfunction				
Adiponectin	8.9 (6.1, 11.0)	8.9 (7.5, 11.5)	n/a	0.46

* Data presented in abstract based on data available by August 16th, 2008

BACKGROUND

- Many HIV-infected children carry cardiovascular disease (CVD) risks.[1,2]
- HIV-infected adults have a several fold increased risk of symptomatic CVD (myocardial infarction and stroke) over adults without HIV. [3,4]
- Inflammation and the inflammatory process are thought to be some of the primary mechanisms for CVD (figure below[5]).
- The extent to which these mechanisms are operational in pediatric HIV is poorly understood.



OBJECTIVES

- To determine if biomarkers of the vascular inflammatory pathway are increased in perinatally HIV-infected children compared to a sociodemographically similar HIV-negative control group
- To determine if these biomarkers are different among HIV-infected children with and without hyperlipidemia

METHODS*

Study Population

Protocol: The Adolescent Master Protocol (AMP), which is part of Pediatric HIV/AIDS Cohort Study (PHACS), is a prospective cohort study conducted at 12 US sites designed to define the impact of HIV infection and antiretroviral therapy on pre-adolescents and adolescents with perinatal HIV infection. Domains that are being investigated include growth and sexual maturation, metabolic risk factors for cardiovascular disease, cardiac function, bone health, neurologic, neurodevelopment, language, hearing and behavioral function, and human papillomavirus (HPV) infection. Children from 7 years of age until their 16th birthday born to HIV-infected mothers are eligible for enrollment into AMP. As of December 16, 2008, there were 319 HIV-infected children and 101 HIV-uninfected enrolled in AMP.

Enrollment: Enrollment began in March 2007. As of December 16, 2008, there were 319 HIV+ and 101 HIV-neg enrolled in AMP.

Definitions and Statistical Methods

We identified a convenience sample of 1) the first 51 HIV+ with hyperlipidemia; 2) the first 49 HIV+ without hyperlipidemia [both groups from the AMP cohort]; and 3) 55 HIV-negative and demographically similar children from Miami.

Hyperlipidemia (HL): defined as >1 of the following: total cholesterol > 200 mg/dL; LDL cholesterol>130 mg/dL; triglycerides>110 mg/dL < 10y or >150 mg/dL 10-19 y; or HDL cholesterol < 35 mg/dL.

Main Outcomes: Biomarkers of vascular dysfunction were measured in all groups and included measures of inflammation (CRP, IL-6, MCP-1); coagulant dysfunction (fibrinogen, P-selectin); endothelial dysfunction (I-CAM-1, V-CAM-1, E-selectin); and metabolic dysfunction (adiponectin).

Analysis: We compared sociodemographic, clinical characteristics and vascular biomarkers across the study groups using Fisher's exact test for categorical variables and Kruskal Wallis for continuous variables. The vascular biomarker values were not normally distributed so each measurement was transformed using log base 10 to improve the distribution. For many of the biomarkers, the distributions were still not normally distributed. Thus, we used the Spearman Rank Test to evaluate the correlations between each biomarker and the fasting lipids. To evaluate the association of each HIV-related variable (CD4, RNA, current PI/NNRTI/NRTI use) with each biomarker, we used generalized estimating (GEE) equations for one record per person (PROC GENMOD), rather than general linear models, to relax the assumptions of normality. PI, NNRTI and NRTI were put in as a group. The final model included HIV-related variables that were significant at P < 0.1 or were confounders of other HIV-related variables in the model. All models were adjusted for age, sex, race/ethnicity and BMI-Z score. We also used PROC GEMOD to compare vascular markers across study groups, adjusted for age, sex, race/ethnicity and BMI-Z score. All analyses were performed in SAS.

* Data presented in poster based on data available by December 16th, 2008

RESULTS

Table 1: Prevalence of hyperlipidemia in AMP cohort (N = 297)*

Variable	N	Percent
Any Hyperlipidemia	125	45%
Total Cholesterol > 200 mg/dl	63	23%
LDL-Cholesterol > 130 mg/dl	42	15%
HDL-Cholesterol <35 mg/dl	37	13%
Triglyceride >110 [<9 y]; > 130 [10-19y]	76	25%

*Available data as of November 30, 2008

Table 2: Baseline characteristics by group

Variable (med. IQR)	HIV + WITH HL (n=51)	HIV + NO HL (n=49)	Controls (n=55)
Age (years)*	12.5 (10.4, 14.1)	12.3 (11, 14.3)	12.1 (9.7. 15.0)
Sex (% male)**	45	49	55
Race (% Black)**	67	73	62
BMI (Z-score)*	0.29 (-0.28, 1.16)	0.08 (-0.42, 1.06)	0.50 (-0.21, 1.48)
CD4 %*	33.6 (27.6, 38.0)	35.4 (31, 40)	N/A
Viral Load (copies/mm³)*	400 (400, 1890)	400 (75, 939)	N/A
% on PI**[,1]	88	71	N/A

*Kruskal-Wallis Test; **Fisher's Exact Test
[1]P=0.046; no other significant differences found

Table 3: Lipid profiles by HIV+ Group

Variable (median, IQR)	HIV + WITH HL (n=51)	HIV + NO HL (n=49)	P-Value*
Total Cholesterol (mg/dL)	205 (175, 220)	158 (141, 179)	<0.001
LDL-Cholesterol (mg/dL)	128 (92, 147)	87 (74, 107)	<0.001
HDL-Cholesterol (mg/dL)	49.0 (40, 57)	50.0 (44, 58)	0.31
Triglyceride <10 y (mg/dL)	131 (93, 149)	67 (58, 86)	0.004
Triglyceride ≥10 y (mg/dL)	151 (102, 185)	83 (53, 118)	<0.001

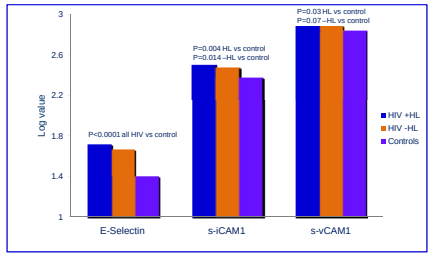
*Kruskal Wallis Test

Table 4: Biomarkers of vascular dysfunction by group, unadjusted*

Median (IQR)	HIV with HL	HIV w/o HL	Controls	Overall P
Inflammation				
CRP	0.40 (0.20, 0.80)	0.40 (0.20, 1.10)	0.20 (0.10, 0.60)	0.13
IL-6	0.90 (0.60, 1.50)	0.90 (0.60, 1.30)	0.80 (0.40, 1.30)	0.20
MCP-1	122 (91.7, 140.7)[1]	105 (84.1, 141.3)	102 (89.5, 122.5)[1]	0.08
Coagulant Dysfunction				
Fibrinogen	398 (361, 425)[1]	375 (328, 424)[2]	334 (282, 377)[1,2]	<0.001
P-Selectin	38.1 (29.5, 50.5)[1]	36.4 (27.3, 55.1)[2]	28.6 (22.3, 35.7)[1,2]	<0.001
Endothelial Dysfunction				
I-CAM-1	307 (237, 381)[1]	286 (244, 352)[2]	231 (162, 253)[1,2]	<0.001
V-CAM-1	750 (646, 948)[1]	759 (642, 933)[2]	682 (578, 841)[1,2]	0.07
E-Selectin	51.4 (40.9, 72.0)[1]	46.8 (33.0 62.4)[2]	24.9 (20.6, 34.4)[1,2]	<0.001
Metabolic Dysfunction				
Adiponectin	8.8 (6.1, 11)	9.0 (6.1, 11)	N/A	0.42

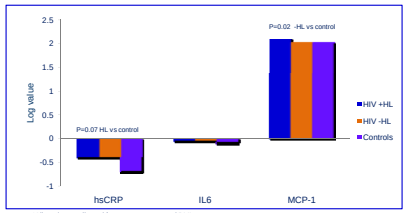
*Kruskal-Wallis Test
[1,2] Biomarkers with like superscripts are significantly different from each other at P<0.05

Figure 1: Differences in measures of endothelial function, adjusted*



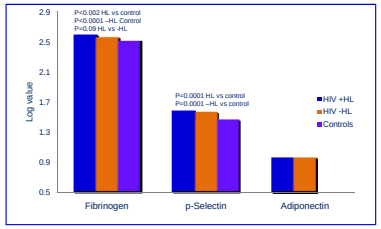
*All analyses adjusted for age, sex, race and BMI

Figure 2: Differences in measures of inflammation, adjusted*



*All analyses adjusted for age, sex, race and BMI

Figure 3: Differences in coagulant and metabolic dysfunction, adjusted*



*All analyses adjusted for age, sex, race and BMI

Additional results and correlations

- Biomarkers consistently correlated with each other
- Few correlations to serum lipid values or HIV disease-specific indicators

CONCLUSIONS

- Biomarkers of vascular inflammation are greater in children with HIV than in a demographically similar group of children
- Differences were greatest in biomarkers reflecting endothelial and coagulant dysfunction
- Biomarkers were not statistically different among HIV+ children with and without hyperlipidemia
- Biomarkers correlated well with each other, but there were few correlations with lipid levels or clinical HIV endpoints
- Future studies should determine longitudinal changes in these biomarkers as well as correlations with disease severity and ART

REFERENCES

[1]Miller TL, Orav EJ, Lipshultz SE, Arheart KL, Duggan C, Weinberg G, Bechard L, Furuta L, Nicchitta J, Gorbach SL, Shevitz A. (2008) Risk factors for cardiovascular disease in human immunodeficiency virus-1 infected children. J Pediatr 153:491-7.

[2]McComsey GA, O'Riordan M, Hazen SL, et al. Increased carotid intima media thickness and cardiac biomarkers in HIV infected children. AIDS. 2007;21:921-7.

[3]DAD Study Group, Friis-Møller N, Reiss P, Sabin CA, et al. Class of antiretroviral drugs and the risk of myocardial infarction. N Engl J Med. 2007, 26;356:1723-35.

[4]Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. J Clin Endocrinol Metab. 2007;92:2506-12.

[5]Libby P. Inflammation in atherosclerosis. Nature 2002; 420: 868–874

ACKNOWLEDGMENTS

Funded by the following National Institutes of Health:

National Institute of Allergy and Infectious Diseases | NIDA | NICHD | NIMH | National Institute on Deafness and Other Communication Disorders | National Heart, Lung and Blood Institute

under cooperative agreements 5U01HD052104-04 (PHACS Coordinating Center, Tulane University) and 1U01HD052102-04 (Data Operations Center, Harvard School of Public Health). We want to thank the Study Participants, Clinical Sites, PHACS CAB, Frontier Science & Technology Research Foundation, Inc., and Westat.