Adipose Mitochondrial Function, Adiponectin, and Insulin Resistance in ACTG A5224s

Todd Hulgan[1,2], Benjamin S. Ramsey[3], John R. Koethe[1,2], David C. Samuels[2], Mariana Gerschenson[4], Daniel E. Libutti[4], Grace A. McComsey[5], Paul E. Sax[6], and Todd T. Brown[7], for the AIDS Clinical Trials Group Study A5224s Team

[1]Vanderbilt Univ. Medical Center and [2]Vanderbilt Univ. School of Medicine, Nashville, TN;[3]Univ. of South Carolina School of Medicine, Greenville, SC; [4]John A. Burns School of Medicine, Univ. of Hawaii-Manoa, Honolulu, HI; [5]Case Western Reserve Univ., Cleveland, OH; [6]Harvard Univ./Brigham & Women's Hospital, Boston, MA; [7]Johns Hopkins Univ., Baltimore, MD.

Contact: todd.hulgan@vanderbilt.edu

Abstract # 691

Introduction

•Some antiretroviral therapy (ART) and perhaps HIV infection itself carry a risk of adverse metabolic effects which may be related, in part, to alterations in mitochondrial function and adipokines.

•A prior AIDS Clinical Trials Group (ACTG) study (**A5224s**; a sub-study of **A5202** [NCT00118898]) found that ART decreased adipose mitochondrial DNA (mtDNA) levels in HIV-infected individuals randomized to initiate two different NRTI regimens with efavirenz or ritonavir-boosted atazanavir, and decreased adipose mitochondrial electron transport chain complex I and complex IV activity in those randomized to TDF/FTC-containing regimens.[1]

•A separate study found an association between a non-synonymous **mtDNA mutation** (10398A>G) and greater decrease in adiponectin (an adipocyte-derived hormone involved in glucose regulation and fatty acid oxidation) after ART initiation.[2]

•We hypothesized that HIV-infected individuals with decreased adipose mitochondrial function on ART will have a corresponding reduction in serum adiponectin and increased insulin resistance, and that these changes will differ by mtDNA mutation 10398A>G.

Methods

•**ACTG A5224s** included metabolic laboratory assessments, fat measurements by DXA and lumbar CT, and excisional fat biopsies from the lower abdomen for a subset of A5202 participants.[1]

•Analyses utilized A5224s data on **adipose mitochondrial complex I and IV activity** and **mtDNA levels** from fat biopsies, and fasting serum **glucose** at baseline and week 96.[1]

•Fasting **insulin and adiponectin levels** were measured from cryopreserved serum using a multiplex immunoassay (Luminex®) at the same time points.

•Insulin resistance and pancreatic beta cell function were estimated by Homeostatic Model Assessment 2 (**HOMA2-IR** and **HOMA2-%B**, respectively).[3]

•The presence of the **mtDNA variant 10398A>G** was determined from existing genome-wide genotype data available from the ACTG DNA Repository (Protocol A5128).

•**Statistical analyses** included Spearman correlation, Wilcoxon ranksum test, and linear regression with single covariate adjustment given the small sample size.

[1]McComsey, et al. *J Infect Dis* 2013; 207:604-11; [2]Hulgan, et al. *AIDS Res Hum Retroviruses* 2013; 29(10): 1293-9; [3]Hill, et al. *Diabetes Care* 2013; 36(8): 2324-30.

Results - 1

•47 A5224s participants had baseline data (**Table 1**).

•Two participants with detectable plasma HIV RNA at week 96 were excluded from longitudinal analyses.

•39 had baseline and week 96 adipose biopsies and serum specimens, and genetic data available (**Table 2**).

Table 1. Baseline Characteristics (N=47)

	Median (IQR) or N (%)
Age- years	**39 (32,45)**
Sex	
Male, N (%)	**42 (89)**
ART, N (%)	
ATVr + ABC-3TC	**10 (21)**
ATVr + TDF-FTC	**13 (28)**
EFV + ABC-3TC	**12 (26)**
EFV + TDF-FTC	**12 (26)**
Plasma HIV-1 RNA (copies/ml)	**63079 (19441,213049)**
CD4+ T cell count (cells/mm³)	**226 (70,312)**
Fat mtDNA (copies/cell)	**1211 (1015,1686)**
Visceral fat (cm²)	**90.9 (69.7,124.3)**
BMI (kg/m²)	**25.7 (21.6,29.9)**
Insulin (µU/ml)	**7.4 (4.7,12.0)**

Table 2. Median (IQR) Baseline, Week 96, and Changes in Adipose Complex IV Activity, Serum Adiponectin, HOMA2-IR, & HOMA2-%B

Complex I activity (OD x 10³/µg)	
Baseline	**46.2 (33.7,53.3)**
Week 96	**36.2 (23.5,52.7)**
Absolute change	**-3.4 (-19.5,6.1)**
% change	**-9.1 (-42.1,18.2)**
Complex IV activity (OD x 10³/µg)	
Baseline	**26.5 (21.4,34.3)**
Week 96	**20.9 (14.9,27.7)**
Absolute change	**-6.1 (-13.5,-.5)**
% change	**-24 (-45,-2)**
Adiponectin (ng/ml)	
Baseline	**7077 (4877,10058)**
Week 96	**7202 (3541,10191)**
Absolute change	**-26 (-2593,1595)**
% change	**-0.3 (-35.7,19.5)**
HOMA2-IR	
Baseline	**0.95 (0.59,1.53)**
Week 96	**1.19 (0.72,1.63)**
Absolute change	**0.23 (-0.23,0.48)**
% change	**36 (-21,66)**
HOMA2-%B	
Baseline	**97 (75,141)**
Week 96	**108 (81,139)**
Absolute change	**13 (-27,30)**
% change	**16 (-25,40)**

Results - 2

Figure 1. Change in adipose complex IV activity correlated with change in serum adiponectin

Percent change in complex IV activity was **positively correlated** with percent change in serum adiponectin.

This association persisted after adjusting for baseline age, sex, BMI, or visceral fat in separate, single-covariate multiple regression analyses (p=0.01-0.03)

Adipose complex I activity was not statistically associated with serum adiponectin.

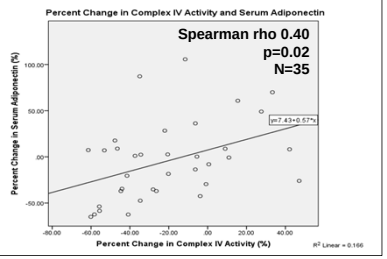


Figure 2. Change in adipose complex I and IV activity correlated with change in HOMA2-IR

Percent change in complex IV activity was **negatively correlated** with percent change in HOMA2-IR.

This relationship was less statistically robust after adjusting for age, BMI, or visceral fat (p=0.05-0.07).

Significant univariate correlations were also observed for complex I and HOMA2-IR (Spearman rho -0.35; p=0.05) and for complex IV and HOMA2-%B (rho -0.36; p=0.04; *data not shown*).

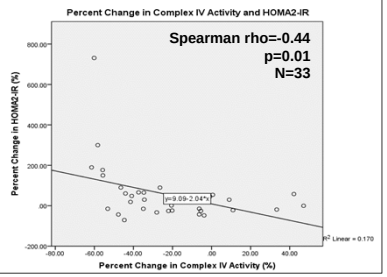
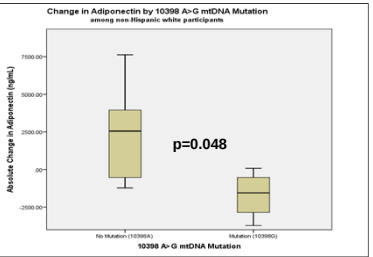


Figure 3. Serum adiponectin decreased in participants with the mtDNA 10398 A>G mutation

Among 12 non-Hispanic white participants, the mtDNA 10398G mutation was associated with absolute change in adiponectin (p=0.048); participants with the mutation had a median decrease in adiponectin (median [IQR] change: -1552 ng/mL [-3286, -223]; N=4) compared to a median increase in participants without the mutation (+2555 ng/mL [-662, 4539]; N=8). This difference remained statistically significant after adjusting for age, sex, BMI, or visceral fat (p=0.03-0.05).



Conclusions

These results suggest that decreased adipose mitochondrial function after ART initiation corresponds to adverse adiponectin and glucose metabolism changes, and (consistent with a prior analysis) the mtDNA 10398A>G mutation may influence this relationship.

The clinical implications of these findings are not known and deserve further study.

The authors acknowledge the participants, sites, and investigators from ACTG study A5202 and A5224s.
A5224s was supported by NIH grants AI065348, AI068636, AI068634, AI38855, AI069434, MD000173, GM007601, and MD007601.
Study medications from A5202 were provided by Abbot Pharmaceuticals, Bristol-Myers Squibb, Gilead Sciences, and GlaxoSmithKline.
Support for the additional assays and analyses used in these analyses was provided by **NIH/NIDDK** (**R21DK101342**).