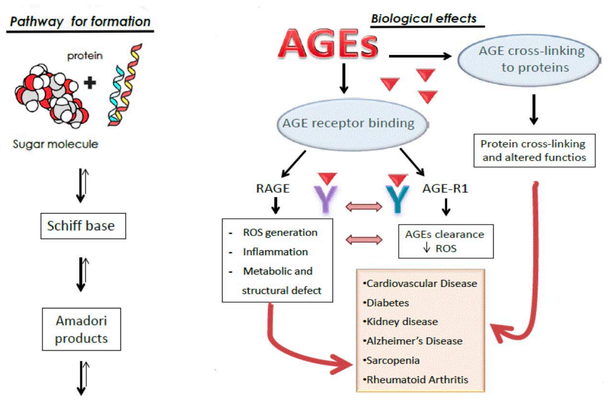
ADVANCED GLYCATION END PRODUCTS ASSOCIATED WITH CARDIOMETABOLIC RISK ON ART

Vanessa El Kamari[1,2], Katherine Rodriguez[3], Carlee Moser[3], Judith S. Currier[4], Theodoros Kelesidis[4], James H. Stein[5], Scott K. Howell[6], Paul Beisswenger[6], Todd Brown[7], Grace A. McComsey[1,2]

[1]Case Western Reserve University, Cleveland, OH; [2]University Hospitals Cleveland Medical Center, Cleveland, OH; [3]Harvard School of Public Health, Boston, MA; [4]University of California Los Angeles, Los Angeles, CA; [5]University of Wisconsin, Madison, WI; [6]Dartmouth College, Hanover, NH; [7]Johns Hopkins University, Baltimore, MD

BACKGROUND



Abate G, et al., J Nutr Food Sci 2015.

- AGEs are implicated in aging and a worsening of many degenerative diseases such as diabetes, atherosclerosis and chronic kidney disease.
- Recent studies showed that AGEs were higher in people with HIV (PWH) compared to controls.

OBJECTIVES

- To assess changes in AGE levels after initiation of ART in treatment-naïve PWH.
- To assess whether AGEs are predictive of increases in insulin resistance, cardiovascular disease risk, and visceral and overall adiposity with newer ART agents.

METHODS

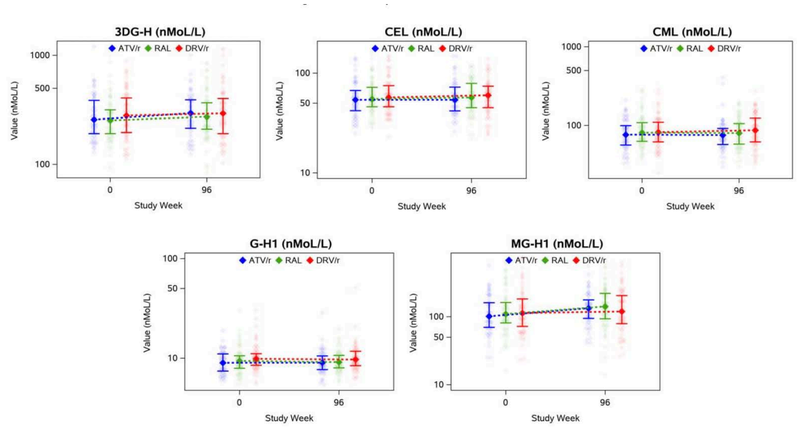
ACTG A5260, a substudy of A5257, is a prospective randomized, open-label trial where treatment-naïve PWH were randomized to receive TDF/FTC plus either ATV/r, DRV/r, or RAL for 96 weeks. 214 participants were included in this analysis; 90% male, 48% white, non Hispanic, with median age of 36 years, HIV-RNA 4.58 log10 copies/mL, and CD4 count of 338 cells//µL.

Study Evaluations:

- Serum levels of five different serum AGEs (CML, MG-H1, 3DG-H, CEL, and G-H1)
- Carotid- Intima Media Thickness (c-IMT)
- Homeostatic Modal Assessment - Insulin Resistance (HOMA-IR)
- Adipokines levels (leptin and adiponectin)
- Visceral, subcutaneous and total adipose tissue (VAT, SAT, and TAT) by CT scan
- Bone mineral density (BMD) at the hip and lumbar spine measured by DEXA scan

RESULTS

CHANGES IN AGE LEVELS OVER TIME BY TREATMENT ARM



- Most AGEs increased following ART initiation, but only MG-H1 levels significantly increased, with no difference between arms
- At baseline, AGEs were positively associated with HOMA-IR, even after confounder adjustment.
- At week 96, additional associations emerged between various AGEs and cIMT, VAT, SAT, total fat, leptin, and adiponectin, even after adjusting for confounders
- No significant associations were observed between AGE levels and HIV variables (CD4+ T cell levels or viral load), nor with BMD measures

REGRESSION ESTIMATES FOR WEEK 96 CHANGES IN MG-H1 AND WEEK 96 CHANGES IN CARDIOMETABOLIC PARAMETERS WHILE ADJUSTING FOR COFOUNDERS

	Leptin	cIMT	HOMA-IR	Lean Mass
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
Unadjusted MG-H1	0.05** (0.0, 0.1)	0.48* (0.0, 0.9)	0.09** (0.1, 0.1)	0.64* (0.1, 1.2)
Adjustment				
Age	0.05** (0.0, 0.1)	0.47* (0.0, 0.9)	0.09** (0.1, 0.1)	0.65* (0.1, 1.2)
Sex	0.05** (0.0, 0.1)	0.48* (0.0, 0.9)	0.09** (0.1, 0.1)	0.69* (0.1, 1.2)
Race/Ethnicity	0.05** (0.0, 0.1)	0.48* (0.0, 0.9)	0.09** (0.1, 0.1)	0.72* (0.1, 1.2)
Smoking history	0.05** (0.0, 0.1)	0.50* (0.0, 0.9)	0.09** (0.1, 0.1)	0.65* (0.1, 1.2)
CD4+ cell count	0.05** (0.0, 0.1)	0.48* (0.0, 0.9)	0.09** (0.1, 0.1)	0.62* (0.1, 1.2)
HIV-1 RNA	0.05** (0.0, 0.1)	0.48* (0.0, 0.9)	0.09** (0.1, 0.1)	0.63* (0.1, 1.2)

[1]Estimates are presented as 0.3 log_{10} units, which is equivalent to a 2-fold difference in MG-H1. Changes of HOMA-IR and leptin are analyzed as absolute difference of log10 transformed markers. All other changes are calculated as percent change.

[2]Only significant associations are shown. Other parameters studied that did not show any significant associations included Adiponectin, L1-L4 BMD, hip BMD, BMI, SAT, VAT, and total fat.

**p≤0.05; **p≤0.001*

CONCLUSION

- Despite virological suppression, ART does not appear to be effective in reducing AGEs levels. On the contrary, AGE levels seem to increase following ART initiation.
- Accumulation of AGEs was found to be independently associated with cardiometabolic complications in treated PWH.
- Further studies are warranted to better understand the pathogenesis leading to increase AGE levels in this population. Further analysis is being done to determine the role of inflammation and immune activation markers on AGE levels.
- Our results have important clinical relevance, suggesting that AGEs might be a new potential therapeutic target for the treatment of non- HIV-associated cardiometabolic comorbidities.