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Soluble Levels of Receptor for Advanced Glycation Endproducts (RAGE) and Progression of Atherosclerosis in Individuals Infected with Human Immunodeficiency Virus: ACTG NWCS 332

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Abstract

Identification of biomarkers and/or mediators of cardiovascular disease (CVD) associated with HIV-infection would be of diagnostic and therapeutic value. As soluble Receptor for Advanced Glycation End Products (sRAGE) and endogenous secretory (esRAGE) have been implicated in vascular complications in other settings, we investigated whether either soluble form of RAGE was associated with changes in carotid intima-media thickness (CIMT) in HIV-infected patients and HIV-uninfected controls. We found no differences in sRAGE, esRAGE, or CIMT among groups at study entry, or in yearly rates of change in sRAGE, esRAGE, or CIMT by HIV-serostatus (all $p>0.10$). However, yearly rates of change in sRAGE ($p=0.07$) and esRAGE ($p<0.001$) were higher in those taking protease inhibitors, and lower baseline esRAGE levels ($p=0.06$) were associated with increased odds of CIMT progression in HIV-infected individuals. Although esRAGE was not altered by HIV-serostatus ($p=0.17$), its inverse relationship with CIMT progression in HIV-infected patients suggests a possible role as a mediator of CVD in HIV-infected persons.

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Summary of Major Findings: This work suggests a possible role for sRAGE and/or esRAGE as mediators of cardiovascular disease in HIV-infected persons.

Keywords

Human Immunodeficiency Virus; Receptor of Advanced Glycation Endproducts; Atherosclerosis; Carotid Intima-Media Thickness

Introduction

Following institution of antiretroviral therapy, cardiovascular disease (CVD) has become a major cause of morbidity and mortality in HIV-infected individuals (1, 2), and the cardiovascular risk appears greater than that predicted by conventional risk factors (1–9). Although a number of biomarkers have been investigated (10–15), including serum biomarkers of microbial translocation (LPS) and macrophage activation (sCD14) by our group (16), identification of additional markers and/or mediators contributing to excess cardiovascular risk would be of great value. The Receptor for Advanced Glycation Endproducts (RAGE) is one potential candidate. RAGE has been implicated in the pathogenesis and progression of chronic diseases such as diabetes, atherosclerosis, and other immune/inflammatory disorders (such as rheumatoid arthritis and sepsis) (17). RAGE is a member of the immunoglobulin superfamily of cell surface molecules, is expressed on multiple cell types (such as endothelial cells, smooth muscle cells, neutrophils, monocytes/macrophages, dendritic cells, T lymphocytes, and B lymphocytes), and binds to and transduces the signal stimulated by a number of ligands [including advanced glycation endproducts, proinflammatory S100/calgranulins, high-mobility group box-1 protein (HMGB1) and amyloid-beta peptide]. In humans, two soluble forms of RAGE are detectable, including soluble [sRAGE, a form of the extracellular receptor cleaved from the cell surface via the actions of various proteases such as a disintegrin and metalloproteinase domain-containing protein 10 (ADAM10) and matrix metalloproteinases (MMPs)] and endogenous secretory [esRAGE, the translation product of a splice variant of RAGE] (17). In animals with atherosclerosis, diabetes, immune/inflammatory activation, or chronic degenerative disorders, antagonism and/or genetic deletion of RAGE is remarkably protective in attenuating cellular stress and tissue damage (18, 19). Numerous studies suggest that circulating levels of soluble RAGEs may serve as biomarkers or mediators of disease activity in humans as well (17, 20). However, in humans, the relationship between RAGE and a variety of adverse outcomes may be more complex than that observed in animal models. Piarulli and colleagues (21) have suggested that, in the setting of cardiovascular complications associated with diabetes in humans, sRAGE levels may change over time with disease activity. They propose that sRAGE levels are high in the early stages of inflammation; levels gradually decline in the intermediate stages (perhaps due to sequestration) and may rise again in the late stages of disease (as a result of increased cleavage and release of cell surface RAGE resulting from inflammation associated with acute cardiovascular events). Additional studies aimed at clarifying the relationship between sRAGE and esRAGE in each stage of disease are essential to identify the mechanistic links between levels of sRAGEs and chronic diseases such as HIV, diabetes, and cardiovascular disease. Interestingly, in some studies, therapeutic interventions with statins, angiotensin converting enzyme (ACE) inhibitors, or calcitrol modulated sRAGE levels; treatment with

these therapeutic agents resulted in higher levels of sRAGE compared to the pre-treatment values (22–24).

Little is known about whether sRAGE or esRAGE is modulated by HIV infection or its treatments, especially PI therapy, which has been implicated in HIV-associated CVD (1–6). Therefore, we utilized stored samples from the previously-reported prospective, matched cohort ACTG A5078 study (25) originally designed to study the role of PI therapy and HIV infection on the risk of development of subclinical atherosclerosis and its progression (as evaluated by progression of carotid intima-media thickness, CIMT) to investigate whether there are associations between HIV infection, PI exposure, CIMT, and the novel inflammatory biomarkers/mediators sRAGE and esRAGE. In accordance with the suggestion of Piarulli and colleagues (21) postulating triphasic levels of sRAGE and esRAGE, we hypothesized that sRAGE and esRAGE levels would be intermediate at baseline in this cohort selected for low cardiovascular risk, but with chronic underlying inflammation resulting from HIV infection, and would increase over time in association with CIMT progression.

Materials and Methods

Study Design

This study is a secondary analysis of the previously reported (25) clinical trial A5078: “Progression of carotid artery intima-media thickening in HIV-infected and -uninfected adults: a pilot study”. Briefly, A5078 was a prospective, matched cohort study designed to investigate the role of PI therapy and HIV infection on the risk of development of subclinical atherosclerosis and its progression, which enrolled 134 individuals into 45 triads (each comprised of three individuals matched for six cardiovascular risk factors including age, sex, race/ethnicity, smoking status, blood pressure, and menopause status) from eight university-based outpatient HIV clinics. Each triad consisted of one individual from each of the following groups: Group 1, HIV-infected individuals with continuous use of PI therapy for ≥2 years (n=44, HIV/PI); Group 2, HIV-infected individuals without prior PI use (<3 cumulative months PI therapy permitted, n=44, HIV/not PI); and Group 3, HIV-uninfected individuals (n=44, not HIV). Baseline and longitudinal measurements, including CIMT, were obtained at weeks 0, 24, 48, 72, 96, and 144. Individuals were excluded if they had diabetes mellitus, family history of early myocardial infarction in first-degree relatives, a history of coronary heart disease or stroke, uncontrolled hypertension, untreated hypothyroidism, or obesity. Individuals requiring systemic chemotherapy, radiation therapy, or systemic steroids were also excluded, as were individuals with a serum creatinine >1.5 mg/dL or alanine or aspartate aminotransferases >2.5× upper limit of normal.

In this secondary analysis utilizing stored A5078 samples, levels of plasma sRAGE and esRAGE were measured at weeks 0, 72, and 144 in individuals who also had HIV RNA <500 copies/mL and CIMT results at all time points (in cases where a week 144 sample was not available, a week 96 sample was utilized, thus referred to as “week 96/144”). The 80 participants who had the required RNA level and sufficient residual sample to be included in this analysis were from 40 triads (Group 1: n=25, Group 2: n=21, and Group 3: n=34), of

which 9 triads were complete. The A5078 informed consent document included the provision for future testing of stored samples for ACTG-approved AIDS-related research.

Data Collection

Fasting glucose, insulin, lipids, cardiovascular/metabolic disease-related measurements (including homocysteine and high-sensitivity C-reactive protein (hs-CRP)), CD4+ cell counts, and HIV-1 RNA levels were collected at A5078 study entry. The CIMT at the far wall of the right distal common carotid artery was measured at baseline and longitudinally (25). In this study, plasma sRAGE and esRAGE levels were assayed on stored samples using enzyme-linked immunosorbent assay (ELISA) kits in accordance with the manufacturer's protocol (R&D Systems Quantikine Immunoassay Minneapolis, MN, and B-Bridge ELISA, B-Bridge International, Cupertino, CA, respectively). Serum sCD14 and LPS were measured on stored samples as previously published (16).

Statistical Methods

In this small, exploratory secondary analysis, results with 2-sided p-values <0.10 were deemed *a priori* as worthy of future investigation; no adjustments were made for multiple comparisons. By-group comparisons of baseline characteristics and biomarkers were assessed using the Fisher's exact, Wilcoxon, and Kruskal-Wallis tests as appropriate. The yearly rate of change in each biomarker was based on three time points for each participant. Using a 48-week year, simple linear regression was used to calculate each participant's yearly rate of change (i.e., slope) in the biomarker (reported in biomarker unit/year). A matched analysis comparing the HIV/PI and HIV/not PI groups (11 matched pairs) assessed the effect of PI therapy on RAGE in the HIV-infected participants using a Wilcoxon test. The comparison of the HIV/not PI and not HIV groups (17 matched pairs; or the combined HIV group against the not HIV group if there was no PI effect; 29 matched pairs/triplets) assessed the effect of HIV infection on RAGE. A variation on the Wilcoxon signed-rank test was used to compare up to two HIV-infected participants with one HIV-uninfected participant (26). Mixed models regression analyses with triad as a random effect evaluated whether baseline measurements of sRAGE and esRAGE were associated with other baseline variables. Repeated measures regression analyses with triad as a random effect evaluated associations with yearly rates of change in sRAGE, esRAGE, and CIMT. Progression of CIMT was defined in A5078 as yearly rate of change ≥12.2 μm/yr. Conditional logistic regression modeling for matched pairs data stratified by triad evaluated associations of baseline variables with the odds of CIMT progression. Variables with $p<0.20$ in the univariable analysis were examined together in multivariable analysis and reduced using the backward elimination method, with the final multivariable model containing variables with $p<0.10$. The final multivariable models were adjusted for fasting glucose, statin use, total cholesterol ≥200 mg/dL, non-HDL cholesterol, and BMI. Regression models were also fit in the HIV-infected and -uninfected subgroups. SAS version 9.2 was used for the statistical analysis.

Results

Baseline Characteristics

Participant characteristics are summarized in Table 1. The participants were 91% male, 75% white/non-Hispanic, and 19% Hispanic, with a median age of 41 years. The median baseline CIMT was 695 μm; there were no differences among the three study groups (p=0.74). The 80 participants in this analysis were similar to the 54 who were excluded, except for race (p=0.051; all five Black participants were excluded) and baseline triglycerides (p=0.036; more participants with triglycerides ≥150 mg/dL were excluded).

Comparisons of sRAGE and esRAGE at Weeks 0, 72, and 96/144 Among Study Groups

There were no differences in sRAGE or esRAGE levels among the three study groups at weeks 0, 72, and 96/144 (all p>0.6; Table 2).

Effect of HIV Serostatus and PI Use on Yearly Rate of Change in sRAGE

There were positive yearly rates of change in sRAGE within the HIV/PI and combined HIV groups (median=35 pg/mL/yr; p=0.07 and 34 pg/mL/yr; p=0.05, respectively; Table 2), with no changes over time within the HIV/not PI and not HIV groups (p=0.25 and 0.14, respectively). In a matched analysis, there was no effect of HIV disease on the yearly rate of change in sRAGE (p=0.60). PI use was associated with a modest increase in yearly rate of change in sRAGE (median of paired differences=52 pg/mL/yr; p=0.08).

Effect of HIV Serostatus and PI Use on Yearly Rate of Change in esRAGE

In contrast to sRAGE, there were positive yearly rates of change in esRAGE within each study group (p<0.001, =0.004, <0.001, respectively; Table 2) and within the combined HIV group (p<0.001). Thus, week 96/144 esRAGE was greater than week 0 esRAGE. The median yearly rates of change in esRAGE in the HIV/PI, HIV/not PI, and not HIV groups were 57 pg/mL/yr, 41 pg/mL/yr, and 43 pg/mL/yr, respectively, and 44 pg/mL/yr in the combined HIV group. Similar to the matched analysis of sRAGE, there was no effect on the yearly rate of change in esRAGE associated with HIV disease (p=0.17). A positive yearly rate of change in esRAGE was observed in those taking PIs (median of paired differences=66 pg/mL/yr; p=0.08).

Relationship Between sRAGE and esRAGE

In univariable regression analysis in all participants, higher baseline sRAGE was associated with higher baseline esRAGE (p<0.001); this was also observed in the HIV-infected and -uninfected participants (both p<0.001) (Supplemental Table 2A. A positive yearly rate of change in esRAGE was associated with higher baseline sRAGE in all participants (p=0.002,) and in HIV-infected participants (p=0.068) in univariable analysis (Supplemental Table 2B).

Relationship Between sRAGE, esRAGE, and Baseline Variables

The adjusted multivariable regression analyses of baseline sRAGE and esRAGE are summarized in all participants and HIV-infected and -uninfected participants in Tables 3A and 3B. In the adjusted multivariable analysis in all participants (Table 3A), higher baseline

sRAGE was associated with lower baseline CIMT (p=0.003), higher baseline esRAGE (p<0.001), and higher BMI (p=0.093). In the adjusted multivariable analysis in HIV-infected participants, only higher baseline esRAGE (p=0.006) remained associated with baseline sRAGE. In the adjusted multivariable analysis in HIV-uninfected participants, higher baseline sRAGE was associated with higher baseline esRAGE (p<0.001) and non-white race (p=0.038).

In the adjusted multivariable analysis in all participants (Table 3A), higher baseline esRAGE was associated with higher baseline sRAGE (p<0.001 and lower BMI (p=0.028). In the adjusted multivariable analyses in HIV-infected and -uninfected participants, only higher baseline sRAGE remained associated with baseline esRAGE (p<0.001 and p<0.001, respectively).

A positive yearly rate of change in esRAGE was associated with lower baseline CIMT (p<0.001), HDL ≥35 mg/dL (p=0.007), higher non-HDL cholesterol (p=0.035), and higher homocysteine (p=0.047) in the adjusted multivariable analysis in all participants (Table 3B). In the adjusted multivariable analysis in HIV-infected participants, HDL ≥35 mg/dL (p=0.055), higher waist-to-hip ratio (p=0.089), and higher insulin (p=0.036) remained associated with a positive yearly rate of change in esRAGE. In HIV-uninfected participants, in the adjusted multivariable analysis, a positive yearly rate of change in esRAGE was associated with lower baseline CIMT (p=0.036), triglycerides <150 mg/dL (p=0.052), and higher hs-CRP (p=0.065).

Progression of CIMT & Yearly Rate of Change of CIMT

In this secondary analysis of A5078, progression of CIMT was present in 38% of participants, with a difference among the three groups (p=0.08): 52% in the HIV/PI group, 19% in the HIV/not PI group, and 38% in the HIV-uninfected group (Table 2). In the HIV-infected participants (Table 3B), the adjusted multivariable analysis showed that increased odds of CIMT progression was associated with higher sCD14 (p=0.043), HDL ≥35 mg/dL (p=0.056), and lower esRAGE (p=0.061). In the HIV-uninfected participants, increased odds of CIMT progression was associated with only non-white race (p=0.078). There was no multivariable model for all participants.

Yearly Rate of Change in CIMT

In this analysis, there were no effects of HIV disease (p=0.87) or PI use (p=0.12) on the yearly rates of change in CIMT in a matched analysis (Table 2). There were positive yearly rates of change in CIMT within the HIV/PI and not HIV groups (both p<0.001) and within the combined HIV group (p=0.002). The median yearly rate of change in CIMT in the HIV/PI, HIV/not PI, and not HIV groups were 13 μm/yr, 6 μm/yr, and 9 μm/yr, respectively, and 8 μm/yr in the combined HIV group.

Discussion

This is the first longitudinal study investigating a role for sRAGE or esRAGE as biomarkers and/or mediators of CVD in HIV-infected and -uninfected individuals. Although glycation differences have been suggested in HIV-infected compared to -uninfected individuals (27–

29), in this small subgroup of 80 A5078 study subjects, we did not find evidence that plasma levels of either form of sRAGE studied here were modulated by HIV status. However, we did find progression of CIMT associated with lower baseline esRAGE levels among those with HIV infection, which is consistent with a previous report in HIV-uninfected, diabetic individuals (30). An inverse relationship between CIMT and sRAGE has also been demonstrated in HIV-uninfected non-diabetic (30) and diabetic (31) persons. In a prospective longitudinal study of Japanese subjects with type 1 diabetes, the investigators also noted an inverse correlation between CIMT and sRAGE and esRAGE, independent of traditional risk factors (33). While no differences by HIV status in the yearly rates of change in sRAGE or esRAGE were found, the yearly rates of change in sRAGE and esRAGE were higher among those taking PIs. In the context of previous studies showing changes in levels of soluble RAGEs in subjects receiving therapies such as statins, ACE inhibitors or calcitrol (22–24), this finding in HIV-infected subjects on PI therapy merits further investigation in larger numbers of subjects.

Our findings are in agreement with the only published report investigating a role for sRAGE in CVD in HIV-infected patients. In the study of Jeong and colleagues (34), the authors suggested that sRAGE may have a protective effect against subclinical atherosclerosis in HIV in a Korean population. They noted that sRAGE levels inversely correlated with subclinical carotid atherosclerosis, as measured by carotid IMT and other metabolic variables in HIV-infected patients receiving ART. It is important to note, however, that no control (HIV-uninfected) group was included in that study and that the study was cross-sectional. In the present longitudinal study, our finding that lower baseline levels of esRAGE were associated with increased odds of CIMT progression in HIV-infected individuals suggests that lower levels of these soluble forms of esRAGE may be a putative biomarker of mechanisms that initiate and/or perpetuate vascular inflammation.

While our study and that of Jeong conducted in HIV-infected subjects show that lower esRAGE and sRAGEs, respectively were associated with higher baseline CIMT levels, there have been conflicting observations in the literature on the general relationship between levels of RAGEs and the presence or extent of cardiovascular disease. In some studies, lower versus higher levels of the sRAGEs appeared to be associated with higher disease burden or clinical status (20, 31). In contrast to our study, many of these studies were of cross-sectional design. We predict that single time point analysis in individual subjects may not take into account the effects of various episodes of acute or sub-acute exacerbations of disease, particularly in the setting of superimposed long-standing chronic diseases such as HIV or diabetes. In addition, the majority of studies do not report the levels of *both* sRAGE and esRAGE.

A number of factors limit the generalizability of this study. Specifically, this cohort's median age was only 41 years and represents a population at lower risk for cardiovascular disease, which may have diminished our ability to differentiate cardiovascular disease in those with HIV infection to those without HIV. This study was not designed to investigate a role for sRAGE and/or esRAGE in CVD among HIV-infected patients with detectable viremia, and the study participants differed by race and baseline triglyceride level from those in the original cohort. It is possible that cryopreservation affected the sRAGE and esRAGE results,

but reassuring in this regard was that the levels we found were in the same range as those noted in other human studies (20). In addition, there are limitations and challenges associated with use of any biomarker (32, 35) and surrogate endpoints (36). However, because of the well-described role of RAGE in atherosclerosis, complications associated with diabetes, as well as other inflammatory disorders, and in view of the chronic inflammation and immune activation associated with HIV and prevalence of CVD beyond that predicted by the Framingham Risk Score, we propose that further investigation of a role for these molecules in the setting of HIV is indicated. Despite the fact that we did not identify an effect due to HIV in this cohort, we did observe that PI use may be associated with positive yearly rates of change of sRAGE and esRAGE, and that HIV-infected subjects with lower baseline esRAGE displayed the most CIMT progression, consistent with some reports in other inflammatory conditions. Additional studies may further elucidate these observations, and/or reveal whether RAGE contributes to or protects against accelerated atherosclerosis in a cohort of HIV-infected persons.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Grinspoon SK, Grunfeld C, Kotler DP, Currier JS, Lundgren JD, Dube MP, et al. State of the science conference: Initiative to decrease cardiovascular risk and increase quality of care for patients living with HIV/AIDS: executive summary. Circulation. 2008; 118:198–210. [PubMed: 18566320]
2. Aberg JA. Cardiovascular Complications in HIV Management: Past, Present, and Future. J Acquir Immune Defic Syndr. 2009; 50:54–64. [PubMed: 19295335]
3. Currier JS, Kendall MA, Zackin R, et al. Carotid artery intima-media thickness and HIV infection: traditional risk factors overshadow impact of protease inhibitor exposure. AIDS. 2005; 19:927–33. [PubMed: 15905673]
4. Law MG, Friis-Moller N, El-Sadr WM, et al. The use of the Framingham equation to predict myocardial infarctions in HIV-infected patients: comparison with observed events in the D:A:D Study. HIV Med. 2006; 7:218–30. [PubMed: 16630034]
5. Friis-Moller N, Thiebaut R, Reiss P, et al. Predicting the risk of cardiovascular disease in HIV-infected patients: the data collection on adverse effects of anti-HIV drugs study. Eur J Cardiovasc Prev Rehabil. 2010; 17(5):491–501. [PubMed: 20543702]
6. D'Agostino RB Sr. Cardiovascular risk estimation in 2012: lessons learned and applicability to the HIV population. J Infect Dis. 2012; 205(Suppl 3):S362–7. [PubMed: 22577209]
7. Jacobson TA, Maki KC, Orringer C, Jones P, Kris-Etherton P, Sikand G, Forge RL, Daniels S, Wilson D, Morris P, Wild R, Grundy S, Daviglus M, Ferdinand K, Vijay K, Deedwania P, Aberg J, Liao K, McKenney J, Ross J, Braun L, Ito M, Bolick J, Dicklin MR, Kirkpatrick C, Rhodes K, Smith NT, Blackett P, DeFerranti S, Gidding S, Kavey R-EW, McCrindle B, McNeal C, Urbina E,

Dayspring T, Underberg JA, Lopez JAG, Pirzada A, Rodriguez CJ, Fichtenbaum CJ, Gallant JE, Horberg MA, Longenecker CT, Myerson M, Overton ET, Coblyn JS, Curtis J, Plutzky J, Solomon D, Bays H, Brown WV. National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 2. Journal of Clinical Lipidology. 2015; doi: 10.1016/j.jacl.2015.09.002

8. Subramanian S, Tawakol A, Burdo TH, Abbara S, Wei J, Vijayakumar J, Corsini E, Abdelbaky A, Zanni MV, Hoffmann U, Williams KC, Lo J, Grinspoon SK. Arterial inflammation in patients with HIV. JAMA. 2012; 308:379–86. [PubMed: 22820791]
9. Post WS, Budoff M, Kingsley L, Palella FJ, Witt MD, Li X, et al. Associations Between HIV Infection and Subclinical Coronary Atherosclerosis. Ann Intern Med. 2014; 160:458–467. [PubMed: 24687069]
10. Kuller LH, Tracy R, Belloso W, De Wit S, Drummond F, Lane HC, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. PLoS Med. 2008; 5:e203. [PubMed: 18942885]
11. Deeks SG. Immune dysfunction, inflammation, and accelerated aging in patients on antiretroviral therapy. Top HIV Med. 2009; 17(4):118–23. [PubMed: 19890183]
12. Aberg JA. Aging, Inflammation and HIV Infection. Top Antivir Med. 2012; 20(3):101–5. [PubMed: 22954610]
13. O'Brien M, Montenont E, Hu L, Nardi MA, Valdes V, Merolla M, Gettenberg G, Frleta D, Cavanagh K, Aberg JA, Bhardwaj N, Berger JS. Aspirin attenuates platelet activation and immune activation in HIV-infected subjects on antiretroviral therapy; a pilot study. J Acquir Immune Defic Syndr. 2013; 63(3):280–8. [PubMed: 23406976]
14. Hunt PW, Sinclair E, Rodriguez E, Shive C, Clagett B, Funderburg N, Robinson J, Huang Y, Epling L, Martin JN, Deeks SG, Meinert CL, Van Natta ML, Lederman MM. Gut Epithelial Barrier Dysfunction and Innate Immune Activation Predict Mortality in Treated HIV Infection. J Infect Dis. 2014; 210(8):1228–38. [PubMed: 24755434]
15. Tenorio AR, Zheng Y, Bosch RJ, Krishnan S, Rodriguez B, Hunt PW, Plants J, Seth A, Wilson CC, Deeks S, Lederman M, Landay A. Soluble markers of inflammation & coagulation, but not T-cell activation, predict non-AIDS-defining morbid events during suppressive antiretroviral therapy. J Infect Dis. 2014; 210(8):1248–59. [PubMed: 24795473]
16. Kelesidis T, Kendall MA, Yang OO, Hodis HN, Currier JS. Biomarkers of microbial translocation and macrophage activation: association with progression of subclinical atherosclerosis in HIV-1 infection. J Infect Dis. 2012; 206(10):1558–67. [PubMed: 23066162]
17. Yan SF, Ramasamy R, Schmidt AM. Soluble RAGE: therapy and biomarker in unraveling the RAGE axis in chronic disease and aging. Biochem Pharmacol. 2010; 79(10):1379–86. [PubMed: 20096667]
18. Hallam, Kellie McCormick; Li, Qing; Ananthakrishnan, Radha; Kalea, Anastasia; Zou, Yu S.; Vedantham, Srinivasan; Schmidt, Ann Marie; Yan, Shi Fang; Ramasamy, Ravichandran. Aldose reductase and AGE-RAGE pathways: central roles in the pathogenesis of vascular dysfunction in aging rats. Aging Cell. 2010; 9(5):776–84. [PubMed: 20670350]
19. Harja, Evis; Bu, De-xiu; Hudson, Barry I.; Chang, Jong Sun; Shen, Xiaoping; Hallam, Kellie; Kalea, Anastasia Z.; Lu, Yan; Rosario, Rosa H.; Oruganti, Sai; Nikolla, Zana; Belov, Dmitri; Lalla, Evanthia; Ramasamy, Ravichandran; Yan, Shi Fang; Schmidt, Ann Marie. Vascular and inflammatory stresses mediate atherosclerosis via RAGE and its ligands in apoE−/− mice. J Clin Invest. 2008; 118(1):183–94. [PubMed: 18079965]
20. Colhoun HM, Betteridge DJ, Durrington P, Hitman G, Neil A, Livingstone S, Charlton-Menys V, Bao W, Demicco DA, Preston GM, Deshmukh H, Tan K, Fuller JH. Total soluble and endogenous secretory receptor for advanced glycation end products as predictive biomarkers of coronary heart disease risk in patients with type 2 diabetes: an analysis from the CARDS trial. Diabetes. 2011; 60(9):2379–85. [PubMed: 21771973]
21. Piarulli F, Sartore G, Lapolla A. Glyco-oxidation and cardiovascular complications in type 2 diabetes: a clinical update. Acta Diabetol. 2013; 50(2):101–110. [PubMed: 22763581]
22. Santilli F, Bucciarelli L, Noto D, Cefalù AB, Davì V, Ferrante E, Pettinella C, Averna MR, Ciabattoni G, Davì G. Decreased plasma soluble RAGE in patients with hypercholesterolemia:

effects of statins. Free Radic Biol Med. 2007; 43(9):1255–62. Epub 2007 Jul 4. [PubMed: 17893038]

23. Forbes JM, Thorpe SR, Thallas-Bonke V, Pete J, Thomas MC, Deemer ER, Bassal S, El-Osta A, Long DM, Panagiotopoulos S, Jerums G, Osicka TM, Cooper ME. Modulation of soluble receptor for advanced glycation end products by angiotensin-converting enzyme-1 inhibition in diabetic nephropathy. J Am Soc Nephrol. 2005; 16(8):2363–72. [PubMed: 15930093]
24. Sung JY, Chung W, Kim AJ, Kim HS, Ro H, Chang JH, Lee HH, Jung JY. Calcitrol treatment increases serum levels of the soluble receptor of advanced glycation end products in hemodialysis patients with secondary hyperparathyroidism. Tohoku J Exp Med. 2013; 230:59–66. [PubMed: 23748365]
25. Currier JS, Kendall MA, Henry WK, Alston-Smith B, Torriani FJ, Tebas P, Li Y, Hodis HN. Progression of carotid artery intima-media thickening in HIV-infected and uninfected adults. AIDS. 2007; 21:1137–45. [PubMed: 17502724]
26. Lehmann, E. Nonparametrics: Statistical Methods based on Ranks. San Francisco: Holden-Day; 1975.
27. Kim P, Woods C, Georgoff P, Crum D, Rosenberg A, Smith M, Hadigan C. A1C Underestimates Glycemia in HIV Infection. Diabetes Care. 2009; 32:1591–3. [PubMed: 19502538]
28. Glesby MJ, Hoover DR, Shi Q, Danoff A, Howard A, Tien P, Merenstein D, Cohen M, Golub E, Dehovitz J, Nowicki M, Anastos K. Glycated haemoglobin in diabetic women with and without HIV infection: data from the Women's Interagency HIV Study. Antivir Ther. 2010; 15(4):571–7. [PubMed: 20587850]
29. Eckhardt BJ, Holzman RS, Kwan CK, Baghdadi J, Aberg JA. Glycated Hemoglobin A(1c) as screening for diabetes mellitus in HIV-infected individuals. AIDS Patient Care STDS. 2012; 26(4): 197–201. [PubMed: 22324292]
30. Lin X, Chen X, Ye J, Li Q, Zhou J, Wu X, Huang Y, Li X, Shi Y, Li S, Li L, Cai H. Association between endogenous secretory receptor for advanced glycation-end products (esRAGE) and carotid intima-media thickness in type 2 diabetes. Exp Clin Endocrinol Diabetes. 2014 May; 122(5):277–80. [PubMed: 24839222]
31. Falcone C, Emanuele E, D'Angelo A, Buzzi MP, Belvito C, Cuccia M, Geroldi D. Plasma levels of soluble receptor for advanced glycation end products and coronary artery disease in nondiabetic men. Arterioscler Thromb Vasc Biol. 2005; 25(5):1032–7. [PubMed: 15731496]
32. Grossin N, Wautier MP, Meas T, Guillausseau PJ, Massin P, Wautier JL. Severity of diabetic microvascular complications is associated with a low soluble RAGE level. Metab. 2008; 34:392–5.
33. Katakami N, Matsuhisa M, Kaneto H, Matsuoka TA, Sakamoto K, Yasuda T, Umayahara Y, Kosugi K, Yamasaki Y. Serum endogenous secretory RAGE level is an independent risk factor for the progression of carotid atherosclerosis in type 1 diabetes. Atherosclerosis. 2009; 204(1):288–92. [PubMed: 18926539]
34. Jeong SJ, Kim CO, Song YG, Baek JH, Kim SB, Jin SJ, Ku NS, Han SH, Choi JY, Lee HC, Kim JM. Low plasma levels of the soluble receptor for advanced glycation end products in HIV-infected patients with subclinical carotid atherosclerosis receiving combined antiretroviral therapy. Atherosclerosis. 2011; 219(2):778–83. [PubMed: 21872861]
35. Leeansyah L, Malone DFG, Anthony DD, Sandberg JK. Soluble biomarkers of HIV transmission, disease progression and comorbidities. Curr Opin HIV AIDS. 2013; 8:117–24. [PubMed: 23274365]
36. Zier, Lucas S., MD, MS; Sottile, Peter D., MD; Hong, Seo Yeon, MBA; Weissfield, Lisa A., PhD; White, Douglas B, MD, MAS. Surrogate Decision Makers' Interpretation of Prognostic Information: A Mixed-Methods Study. Ann Intern Med. 2012; 156(5):360–366. [PubMed: 22393131]

Table 1

Participant Characteristics

Except otherwise indicated, data represent N (%) of participants.

Variable	Total (n=80)	HIV Infected		Not HIV (n=34)
		HIV/PI (n=25)	HIV/Not PI (n=21)	
Male sex	73 (91)	24 (96)	19 (90)	30 (88)
Race or ethnicity				
White non-Hispanic	60 (75)	20 (80)	15 (71)	25 (74%)
Hispanic (regardless of race)	15 (19)	3 (12)	4 (19)	8 (24%)
Other/unknown	5 (6)	2 (8)	2 (10)	1 (3)
Age, median (IQR), y	41 (36, 45)	41 (37, 45)	41 (38, 45)	40 (36, 45)
BMI, median (IQR), kg/m^2	24.7 (23.4, 27.2)	24.7 (23.4, 27.6)	24.4 (23.4, 26.6)	24.8 (23.7, 27.7)
Waist circumference ≥ 90 cm[a]	36 (46)	14 (58)	7 (33)	15 (44)
Waist-to-Hip Ratio, median (IQR)	0.90 (0.85, 0.93)	0.93 (0.91, 0.95)	0.90 (0.87, 0.93)	0.89 (0.83, 0.92)
Any statin use	7 (9)	6 (24)	1 (5)	0 (0)
Metabolic parameters				
Fasting blood glucose, median (IQR), mg/dL	86 (79, 93)	87 (81, 94)	84 (81, 92)	86 (75, 92)
Total cholesterol ≥ 200 mg/dL	38 (48)	19 (76)	6 (29)	13 (38)
Direct LDL cholesterol ≥ 100 mg/dL[b]	55 (69)	19 (76)	13 (62)	23 (68)
HDL cholesterol < 35 mg/dL	18 (23)	5 (20)	6 (29)	7 (21)
Triglycerides ≥ 150mg/dL	31 (39)	15 (60)	7 (33)	9 (26)
Non-HDL cholesterol, median (IQR), mg/dL	147.5 (122.0, 185.5)	187 (144, 210)	129 (118, 151)	145 (122, 168)
Insulin, median (IQR), mU/L[c]	6.4 (5.1, 8.0)	6.9 (5.8, 13.0)	5.7 (4.6, 7.8)	6.1 (5.0, 7.7)
Inflammation parameters				
hs-CRP, median (IQR), mg/L[c]	1.00 (0.50, 2.10)	1.40 (0.80, 3.30)	0.90 (0.40, 3.40)	0.90 (0.50, 1.70)
Homocysteine, median (IQR), μmol/L[c]	8.95 (7.40, 10.10)	8.90 (7.40, 13.80)	7.45 (6.25, 8.35)	9.70 (8.70, 11.00)
HIV disease-related parameters				
Baseline CD4+ T-cell count, median (IQR), cells/mm^3	515 (344, 679)	559 (395, 707)	469 (329, 642)	…
Nadir CD4+ T-cell count ≤ 200 cells/mm^3 [d]	17 (38)	9 (38)	8 (38)	…
Duration of PI use, median (IQR), wk	126 (0, 244)	238 (152, 259)	0 (0, 0)	…
Baseline sCD14, median (IQR), μg/mL	1.74 (1.08, 2.57)	2.36 (1.69, 3.15)	2.08 (1.64, 2.70)	1.19 (0.95, 1.79)
Baseline CIMT, median (IQR), μm [e]	695 (621, 762)	752 (612, 780)	697 (671, 747)	683 (624, 756)

[a] Because of missing data, the sample sizes were n=79, n=24, n=21, and n=34, respectively.

[b] Because of missing data, the sample sizes were n=78, n=23, n=21, and n=34, respectively.

[c] Because of missing data, the sample sizes were n=74, n=23, n=20, and n=31, respectively.

[d] Because of missing data, the sample sizes were n=45, n=24, and n=21, respectively.

[e] Kruskal-Wallis Test for between group differences in baseline CIMT (p=0.74).

Table 2

Summary of sRAGE, esRAGE, and CIMT Results

	Group					
Variable [Median (Q1, Q3) or N (%)]	**Total (N=80)**	**HIV/PI (N=25)**	**HIV/not PI (N=21)**	**not HIV (N=34)**	**Combined HIV (N=46)**	**P-Value**
Week 0 sRAGE (pg/mL)	1,039 (797, 1,298)	1,053 (779, 1,450)	1,075 (820, 1,416)	1,030 (797, 1,265)	1,064 (792, 1,433)	0.81 [a]
Week 72 sRAGE (pg/mL)	1,062 (835, 1,468)	1,006 (840, 1,427)	1,103 (880, 1,534)	1,069 (830, 1,458)	1,033 (840, 1,478)	0.85 [a]
Week 96/144 sRAGE (pg/mL)	1,136 (805, 1,565)	1,327 (708, 1,823)	1,128 (936, 1,507)	990 (758, 1,561)	1,162 (852, 1,658)	0.65 [a]
Yearly Rate of Change in sRAGE (per pg/mL/yr)	32 (−43, 99)	35 (−46, 157)	33 (−40, 81)	24 (−42, 92)	34 (−46, 114)	0.60 [b]; **0.08** [c]
P-Value [d]		**0.07**	0.25	0.14	**0.05**	
Week 0 esRAGE (pg/mL)	233 (139, 337)	213 (143, 343)	234 (145, 314)	236 (128, 343)	229 (143, 331)	0.95 [a]
Week 72 esRAGE (pg/mL)	299 (175, 478)	220 (155, 471)	301 (171, 421)	327 (207, 481)	266 (156, 471)	0.74 [a]
Week 96/144 esRAGE (pg/mL)	362 (231, 538)	377 (218, 663)	351 (257, 437)	350 (234, 565)	374, 219, 527)	0.86 [a]
Yearly Rate of Change in esRAGE (per pg/mL/yr)	43 (9, 72)	57 (15, 107)	41 (−5, 64)	43 (19, 66)	44 (−2, 74)	0.17 [e]; **0.08** [f]
P-Value [d]		**<0.001**	**0.004**	**<0.001**	**<0.001**	
Progression of CIMT (≥ 12.2 μm/yr)	30 (38%)	13 (52%)	4 (19%)	13 (38%)	17 (37%)	**0.08**[g]
Yearly Rate of Change in CIMT(μm/y)	9 (1, 14)	13 (1, 16)	6 (−7, 10)	9 (4, 15)	8 (−2, 13)	0.87 [h]; 0.12 [i]
P-Value [d]		**<0.001**	0.43	**<0.001**	**0.002**	

[a] Kruskal-Wallis Test testing the difference among the HIV/PI, HIV/not PI, and not HIV groups.

[b] Wilcoxon Test for matched group differences within each visit week testing HIV versus not HIV ("HIV effect"; N=29 matched pairs/triplets).

[c] Wilcoxon Test for matched group differences within each visit week testing PI versus not PI ("PI effect"; N=11 matched pairs). The median (Q1, Q3) of the paired differences was 52 (−22, 282) pg/mL/yr.

[d] Wilcoxon Test for zero yearly rate of change within each group.

[e] Wilcoxon Test for matched group differences within each visit week testing HIV versus not HIV ("HIV effect"; N=29 matched pairs/triplets).

[f] Wilcoxon Test for matched group differences within each visit week testing PI versus not PI ("PI effect"; N=11 matched pairs). The median (Q1, Q3) of paired differences was 66 (8, 89) pg/mL/yr.

[g] Fisher's Exact Test.

[h] Wilcoxon Test for matched group differences within each week testing HIV versus not HIV ("HIV effect"; N=29 matched pairs/triplets).

[i] Wilcoxon Test for matched group differences within each week testing HIV/PI versus HIV/not PI ("PI effect"; N=11 matched pairings).

Table 3A

Summary of Adjusted Multivariable Analysis of Factors Associated with sRAGE, esRAGE, and CIMT Progression.The reference group used for determination of the parameter estimate was clarified as needed. In univariable analysis, the baseline variables considered for all participants were age, sex, race, HIV status, body mass index (BMI), waist circumference, waist/hip ratio, fasting lipid measurements [glucose, total cholesterol, low density lipoprotein (LDL) cholesterol, HDL cholesterol, triglycerides, non-HDL cholesterol, and insulin], use of lipid lowering drugs, use of statins, inflammatory measurements [high-sensitivity C-reactive protein (hs-CRP) and homocysteine], sCD14, LPS, sRAGE, esRAGE, and CIMT. P<0.2 for all variables in univariable analyses were used to create a full multivariable model. The final multivariable models were adjusted for fasting glucose, use of statins, total cholesterol ≥200 mg/dL, non-HDL cholesterol, and BMI.

Variable	All Participants (N=80)		HIV-Infected Participants (N=46)		HIV-Uninfected Participants (N=34)	
	Baseline sRAGE (per 100 pg/mL)					
	Parameter Estimate (90% CI)	**Parameter Estimate (90% CI)**	**Parameter Estimate (90% CI)**	**P-value**	**Parameter Estimate (90% CI)**	**P-value**
Baseline CIMT (per μm)	−0.01 (−0.02, −0.01)	0.003	(−)	(−)	(−)	(−)
Baseline esRAGE (per 100 pg/mL)	2.78 (2.45, 3.11)	<0.001	2.89 (2.24, 3.55)	0.006	2.50 (1.97, 3.04)	<0.001
Non-White Race versus White Race	(−)	(−)	(−)	(−)	2.55 (0.56, 4.54)	0.038
HDL Cholesterol < 35 mg/dL	(−)	(−)	1.52 (−3.73, 0.70)	0.18	(−)	(−)
Body Mass Index (per kg/m^2)	0.20 (0.004, 0.39)	0.093	(−)	(−)	(−)	(−)
Reported Nadir CD4 ≤ 200 cells/mm^3	(−)	(−)	−1.67 (−3.42, 0.08)	0.109	(−)	(−)
	Baseline esRAGE (per 100 pg/mL)					
Baseline sRAGE (per 100 pg/mL)	0.26 (0.23, 0.29)	<0.001	0.025 (0.021, 0.31)	<0.001	0.28 (0.22, 0.34)	<0.001
Body Mass Index (per kg/m^2)	−0.08 (−0.13, −0.02)	0.028	−0.08 (−0.16, 0.0002)	0.101	(−)	(−)
Waist Circumference ≥ 90 cm	(−)	(−)	(−)	(−)	−0.79 (−1.92, 0.34)	0.24

Table 3B

Summary of Adjusted Multivariable Analysis of Factors Associated with sRAGE, esRAGE, and CIMT Progression, Continued.

Yearly Rate of Change in esRAGE (per 100pg/mL/yr)†						
Variable	**All Participants (N=80)**		**HIV-Infected Participants (N=46)**		**HIV-Uninfected Participants (N=34)**	
	Parameter Estimate (90% CI)	**P-value**	**Parameter Estimate (90% CI)**	**P-value**	**Parameter Estimate (90% CI)**	**P-value**
Baseline CIMT (per μm)	−0.003 (−0.004, −0.001)	<0.001	−0.002 (−0.004, 0.0001)	0.124	−0.003 (−0.005, −0.001)	0.036
HDL Cholesterol < 35 mg/dL	−0.36 (−0.58, −0.14)	0.007	−0.48 (−0.89, −0.07)	0.055	(−)	(−)
Triglycerides ≥ 150 mg/dL	(−)	(−)	−0.50 (−1.07, 0.06)	0.142	−0.44 (−0.82, −0.07)	0.052
Non-HDL Cholesterol (per 10 mg/dL)	0.05 (0.01, 0.08)	0.035	0.03 (−0.03, 0.10)	0.394	(−)	(−)
Waist-to-Hip Ratio (per 0.1 unit)	(−)	(−)	0.34 (0.01, 0.66)	0.089	(−)	(−)
hs-CRP (per 10 mg/L)	(−)	(−)	(−)	(−)	0.35 (0.04, 0.65)	0.065
Insulin (per 10 mU/L)	(−)	(−)	0.50 (0.11, 0.89)	0.036	(−)	(−)
Homocysteine (per 10 umol/L)	0.22 (0.04, 0.39)	0.047	(−)	(−)	(−)	(−)
Progression of CIMT						
Variable	Odds Ratio Estimate (90% CI)	P-value	Odds Ratio Estimate (90% CI)	P-value	Odds Ratio Estimate (90% CI)	P-value
Baseline esRAGE (per 100 pg/mL)	(−)	(−)	0.45 (0.007, 0.40)	0.061	(−)	(−)
sCD14 (per μg/mL)	(−)	(−)	2.91 (1.22, 6.92)	0.043	(−)	(−)
HDL Cholesterol < 35 mg/dL	(−)	(−)	0.05 (0.004, 0.65)	0.056	(−)	(−)

†The multivariable models for Yearly Rate of Change in esRAGE included 74, 43, and 31 participants, respectively, with complete data.