Title

Lipoprotein(a) and HIV

Journal

Arteriosclerosis Thrombosis and Vascular Biology, 37(5)

ISSN

1079-5642

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Publication Date

2017-05-01

DOI

10.1161/atvbaha.117.309137

Peer reviewed

HHS Public Access

Author manuscript

Arterioscler Thromb Vasc Biol. Author manuscript; available in PMC 2018 May 01.

Published in final edited form as:

Arterioscler Thromb Vasc Biol. 2017 May ; 37(5): 997–1004. doi:10.1161/ATVBAHA.117.309137.

Lp(a) and HIV: Allele-specific apo(a) levels predict carotid intima media thickness in HIV-infected young women in the Women's Interagency HIV Study

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Abstract

Objective—In the general population, lipoprotein(a), Lp(a), has been established as an independent causal risk factor for cardiovascular disease (CVD). Lp(a) levels are to a major extent regulated by a size polymorphism in the apolipoprotein(a), apo(a), gene. The roles of Lp(a)/apo(a) in HIV-related elevated CVD risk remain unclear.

Approach and Results—The associations between total plasma Lp(a) level, allele-specific apo(a) level, an Lp(a) level carried by individual apo(a) alleles, and common carotid artery intima-

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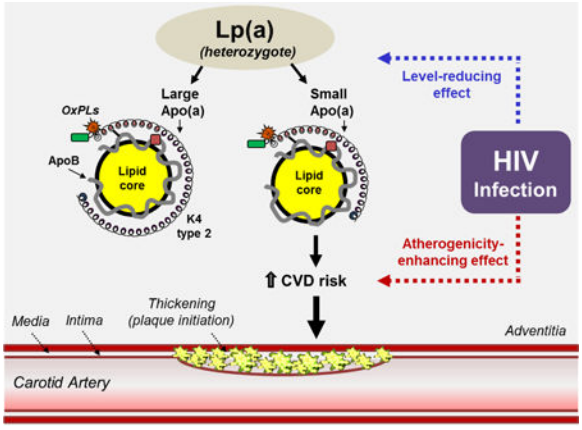
Disclosures: The authors have nothing to disclose.

media thickness (cIMT) were assessed in 150 HIV-infected and 100 HIV-uninfected women in the Women's Interagency HIV Study. Linear regression analyses with and without adjustments were used. The cohort was young (mean age: ~31 years) with the majority being African-Americans (~70%). The prevalence of a small size apo(a) (≤22 Kringle repeats) or a high Lp(a) level (≥30 mg/dL) was similar by HIV status. Total plasma Lp(a) level (p=0.029) and allele-specific apo(a) level carried by the smaller apo(a) sizes (p=0.022) were significantly associated with cIMT in the HIV-infected women only. After accounting for confounders (age, race, smoking, BMI, blood pressure, HCV co-infection, menopause, plasma lipids, treatment status, CD4+ T-cell count, and HIV/RNA viral load), the association remained significant for both Lp(a) (p=0.035) and allele-specific apo(a) level carried by the smaller apo(a) sizes (p=0.010) in the HIV-infected women. Notably, none of the other lipids/lipoproteins was associated with cIMT.

Conclusions—Lp(a) and allele-specific apo(a) levels predict cIMT in HIV-infected young women. Further research is needed to identify underlying mechanisms of an increased Lp(a) atherogenicity in HIV infection.

Graphic Abstract

A schematic model showing the hypothesized role of Lp(a) in carotid intima media thickening in HIV infection. Reflecting the extensive size heterogeneity in the apo(a) gene, the majority of individuals have two different Lp(a) particle populations in the circulation. In general, Lp(a) particles carrying smaller apo(a) sizes are more atherogenic, advancing the atherosclerotic process. Allele-specific apo(a) levels were lower under HIV condition, and a positive correlation was seen between Lp(a) levels carried by smaller apo(a) sizes and carotid intima media thickness.



Keywords

Lipoprotein(a); Apolipoprotein(a); Carotid Artery Intima Media Thickness; Cardiovascular Risk; Apo(a) Size; HIV Treatment; Antiretroviral Therapy

Subject codes

Biomarkers; Clinical Studies; Lipids and Cholesterol; Women; Atherosclerosis; Genetics

INTRODUCTION

Individuals infected with human immunodeficiency virus are at significantly increased risk for cardiovascular disease (CVD) compared to uninfected individuals.[1–3] HIV infection is associated with a 50–100% greater risk of CVD beyond that explained by traditional risk factors, such as hypertension, smoking, and cholesterol level.[4] In a cohort without traditional CVD risk factors, the risk for acute myocardial infarction was 2-fold higher in HIV-infected individuals compared to HIV-uninfected individuals.[5] In a meta-analysis, HIV, treatment status and type and disease activity were associated with CVD risk.[3] Taken together, these findings point out the presence of a significant deficit in the understanding of HIV-related excess CVD risk and the need to identify more contributing factors.

In the general population, an elevated level of plasma lipoprotein(a), Lp(a), is established as an independent causal risk factor for CVD and recognized in clinical guidelines.[6–9] Lp(a) levels are to a major extent regulated by genetics, where a size polymorphism in the apolipoprotein(a), apo(a), gene accounts for the majority of the genetic variability in Lp(a) level.[10] Apo(a), a key structural component of Lp(a), consists of repeated loop structures, termed Kringles (K); one of these K motifs (i.e., K4 type 2) exists in multiple copies.[11, 12] In general, smaller apo(a) sizes with fewer K4 type 2 repeats are associated with higher plasma Lp(a) levels.[10] Lp(a) levels vary across ethnicity/race with the most profound differences between populations of African vs. non-African (e.g., European) descents.[13–15] Further, carriers of smaller apo(a) isoforms (≤22 K4 type 2 repeats) have a 2-fold higher risk of coronary heart disease (CHD) or ischemic stroke than non-carriers.[16] Despite these advances in the general population, less is known about the roles of Lp(a) level and apo(a) size polymorphism in HIV-related CVD development.

In the general population, we previously demonstrated that the allele-specific apo(a) level, an Lp(a) level associated with a defined apo(a) isoform size for a given individual, can inform CHD risk assessment.[17] In a subsequent study in an HIV-infected population, we showed an increase in the allele-specific apo(a) level carried by smaller apo(a) sizes in a group with improved disease status.[18] As the extent of association between a risk factor and disease might vary by HIV status, we investigated the ability of Lp(a) and allele-specific apo(a) levels to predict carotid intima media thickness (cIMT) in HIV-infected women enrolled in the Women's Interagency HIV Study (WIHS). We further tested the effects of HIV treatment status on the associations of Lp(a) or allele-specific apo(a) levels with cIMT.

MATERIALS AND METHODS

Materials and Methods are available in the online-only Data Supplement.

RESULTS

Characteristics of study population

The mean age was ~31 years (age range: 21–37 years) and the cohort predominantly consisted of African-Americans (~70%) (Table 1). HIV-infected women had a lower body mass index (BMI) (p=0.045) and a higher diastolic blood pressure (p=0.029) compared to

HIV-uninfected women. Among the HIV-infected women, 37% had a CD4+ T cell count less than 350 cells/mm^3. Further, 39% of all HIV-infected women had an HIV RNA viral load below or at the lower detection limit (i.e., 80 copies). The average duration of HIV infection was 8.7 ± 3.5 years. The use of medications for heart disease, hypertension, or diabetes was low regardless of HIV status (2–4%). Among the HIV-infected women, 11 (7%) reported any type of statin use. The rate of current smokers was high (41% and 33% in the HIV-infected and HIV-uninfected group, respectively). The majority of women (~97%) were free of HCV co-infection. HIV-infected women had a significantly lower high density lipoprotein cholesterol (HDL-C) (p<0.0001) and a higher triglyceride (p<0.0001) level compared to HIV-uninfected women (Table 1). The mean carotid artery intima media thickness (cIMT) was significantly lower in the HIV-infected vs. HIV-uninfected group (645 ± 70 μm vs. 670 ± 80 μm, respectively, p=0.014), and only one HIV-infected and two HIV-uninfected women had a presence of carotid lesions.

Of the HIV-infected women, about half (51%, n=76) were on treatment, with 73 (96%) receiving highly active antiretroviral therapy (HAART), two (2.6%) receiving combination therapy and one (<1%) receiving monotherapy. Among those on HAART, 44 (60%) women were on protease inhibitor-based regimens and 29 (40%) women were on non-nucleoside reverse transcriptase inhibitor-based or nucleoside reverse transcriptase inhibitor-based regimens. Treated HIV-infected women were slightly older and had a lower BMI compared to untreated HIV-infected women. The median nadir CD4+ T cell count was 330 cells/mm^3 [interquartile range (IQR): 194–396 cells/mm^3] vs. 403 cells/mm^3 (IQR: 289–515 cells/mm^3) in the treated vs. untreated HIV-infected women, respectively. Total cholesterol (p=0.005) and HDL-C (p<0.0001) levels were higher in the treated vs. untreated group. Of note, there was no significant difference in cIMT across treated and untreated groups.

Lp(a) and allele-specific apo(a) levels and apo(a) phenotypes

The median total plasma Lp(a) level (19 mg/dL vs. 25 mg/dL, p=0.024) and allele-specific apo(a) level carried by the smaller apo(a) sizes (14 mg/dL vs. 19 mg/dL, p=0.037) were significantly lower in the HIV-infected vs. HIV-uninfected women (Table 2) (Supplemental Figure I). The frequency of a high Lp(a) level (≥30 mg/dL) was 32% and 43% in the HIV-infected and HIV-uninfected group, respectively. The difference across HIV status for the prevalence of a high Lp(a) level (≥50 mg/dL) reached a borderline significance (17% vs. 27% for the HIV-infected and HIV-uninfected group, respectively, p=0.057). As expected, the majority of individuals had two detectable apo(a) protein bands (>70%). The distribution pattern of apo(a) phenotypes (i.e., single or double) did not differ significantly by HIV status, and the median sizes for the larger or smaller apo(a) isoforms were similar in the HIV-infected and HIV-uninfected groups (Table 2). Among individuals with double apo(a) protein bands, the majority had a co-dominating (41%) or a smaller dominating (~50%) pattern, and the distribution pattern of apo(a) dominance did not differ significantly by HIV status. In both HIV-infected and HIV-uninfected groups, approximately 18% of women had a small size apo(a) (≤22K).

Analyses among HIV-infected women across treatment status revealed no significant differences in total plasma Lp(a) and allele-specific apo(a) levels, frequency of high Lp(a)

level or a small size apo(a), and distribution patterns of apo(a) phenotypes or dominance between treated and untreated group (Table 2). The median apo(a) size for the smaller allele was slightly larger in the treated vs. untreated HIV-infected women (27K vs. 25K, p=0.026).

Associations of carotid artery intima media thickness with clinical variables

As expected, age was a significant predictor of cIMT in both HIV-uninfected (p<0.0001) and HIV-infected (p=0.0007) groups (Table 3). In addition, CD4+ T-cell count (p=0.033) in the HIV-infected group and systolic blood pressure (p=0.0002) and glucose (p=0.002) in the HIV-uninfected group were significantly associated with cIMT. However, none of the major lipids and lipoproteins was significantly associated with cIMT (Table 3).

Associations of carotid artery intima media thickness with Lp(a) or allele-specific apo(a) levels

Next, we tested the ability of Lp(a) and allele-specific apo(a) levels to predict cIMT across HIV status. Notably, total plasma Lp(a) level was significantly associated with cIMT in the HIV-infected group, (β=0.00542, 95% CI: 0.00057, 0.01026; p=0.029), but not in the HIV-uninfected group (β=0.00175, 95% CI: −0.00458, 0.00809; p=0.584) (Table 4) (Supplemental Figure II). Analyses based on allele-specific apo(a) levels revealed a significant association between cIMT and allele-specific apo(a) level carried by the smaller apo(a) size in the HIV-infected group only (β=0.00074, 95% CI: 0.00011, 0.00138; p=0.022). After accounting for confounders, including age, ethnicity/race, current smoking, BMI, blood pressure, HCV co-infection, menopause, LDL-C, HDL-C, triglycerides, HIV therapy, CD4+ T-cell count, and HIV RNA viral load, the association remained significant in the HIV-infected group for both Lp(a) (β=0.00563, 95% CI: 0.00042, 0.01085; p=0.035) and allele-specific apo(a) level carried by the smaller apo(a) size (β=0.00088, 95% CI: 0.00022, 0.00154; p=0.010).

Effect of HIV treatment status on the associations of carotid artery intima media thickness with Lp(a) or allele-specific apo(a) levels

We further examined the impact of HIV treatment status on the associations of cIMT with total plasma Lp(a) or allele-specific apo(a) levels in HIV-infected women. We observed a significant correlation of Lp(a) level with cIMT in the treated HIV-infected women (β=0.00775, 95% CI: 0.00156, 0.01392; p=0.015), but not in untreated HIV-infected women (β=0.00247, 95% CI: −0.00526, 0.01021; p=0.528) (Table 4) (Supplemental Figure I). Similarly, allele-specific apo(a) level carried by the smaller apo(a) size was significantly associated with cIMT in the treated group only (β=0.00091, 95% CI: 0.00012, 0.00170; p=0.025). In a model adjusted for potential confounders (age, ethnicity/race, current smoking, BMI, blood pressure, HCV co-infection, menopause, LDL-C, HDL-C, triglycerides, CD4+ T-cell count and HIV RNA viral load), both total plasma Lp(a) (β=0.00696, 95% CI: 0.00054, 0.01338; p=0.036) and allele-specific apo(a) level carried by the smaller apo(a) size (β=0.00101, 95% CI: 0.00019, 0.00183; p=0.018) remained significantly associated with cIMT in the HIV-infected treated group.

DISCUSSION

This is the first study to examine the associations of Lp(a) and allele-specific apo(a) levels with cIMT in relation to apo(a) isoform sizes and HIV treatment status. The major novel findings in this study of HIV-infected and HIV-uninfected young women are: 1) significant associations of Lp(a) or allele-specific apo(a) levels carried by the smaller apo(a) sizes with cIMT were observed in the HIV-infected group, but not in the HIV-uninfected group; and 2) an impact by HIV treatment status on the association of Lp(a) or allele-specific apo(a) level carried by the smaller apo(a) sizes with cIMT was seen. Notably, adjustments for covariates did not alter the significant associations of Lp(a) or allele-specific apo(a) levels with cIMT in the HIV-infected group. Furthermore, there were no significant differences in the frequency of high Lp(a) level or small size apo(a) (≤22K) and distribution patterns of apo(a) expression or apo(a) dominance across HIV or treatment status.

HIV-infected individuals are at significantly elevated risk of atherosclerosis and CVD compared to HIV-uninfected individuals.[1–3] Infection with HIV causes persistent immune activation associated with CD4+ T-cell loss, HIV RNA viral load, and disease progression, as well as a number of significant anthropometric and metabolic alterations, including dyslipidemia.[19] While HIV/ART-induced modifications in lipids and lipoproteins and their relationships with CVD have been investigated previously,[20] documentation of any role of plasma Lp(a) level and genetic variability in the apo(a) gene (e.g., a size polymorphism) in HIV-related elevated CVD risk is lacking. A small longitudinal study reported an increase in Lp(a) level from baseline among protease inhibitor treated HIV-infected individuals[21]. In a previous study among HIV-infected individuals, we found an elevated allele-specific apo(a) level carried by the atherogenic smaller apo(a) size in the group with an improved HIV disease status.[18] This observation suggested that although considered as one of the most heritable quantitative traits in humans,[10] Lp(a) level and associated risk factor properties can be modulated by HIV disease status, a clinically relevant non-genetic factor, and thus may potentially contribute to the high CVD risk seen in HIV-infected individuals. In the current study, despite a lower Lp(a) level and a comparable distribution of apo(a) isoforms in the HIV-infected vs. HIV-uninfected group, cIMT was associated with Lp(a) only in the HIV-infected group. Similarly, allele-specific apo(a) levels for smaller apo(a) sizes were lower in the HIV-infected vs. HIV-uninfected group, but were associated with cIMT in the HIV-infected group. These findings suggest that HIV may play a modulatory role independent of apo(a) size polymorphism and that HIV-specific mechanisms are contributing to enhance Lp(a) atherogenicity. It is tempting to speculate that the high frequency of untreated HIV-infected women may have contributed to the overall lower Lp(a) level seen in the HIV-infected group.

In several of our previous studies in the general population, we demonstrated a significant positive association between metabolic abnormalities assessed by elevated levels of systemic and vascular inflammatory biomarkers and Lp(a) or allele-specific apo(a) levels.[22–24] HIV-induced persistent immune activation and heightened inflammation have been associated with increased premature age-related comorbidities, including CVD, in HIV-infected individuals.[25–28] With the use of ART inflammatory burden declines; however, inflammatory biomarkers remain high compared to those in HIV-uninfected

individuals.[29–31] It is tempting to speculate that this residual post-ART higher burden of metabolic disturbance promotes Lp(a) atherogenicity in the setting of HIV infection. Furthermore, in the circulation, proinflammatory and proatherogenic oxidized phospholipids (OxPLs) bind to Lp(a) with a substantially greater affinity than other plasma lipoproteins.[32] Thus, the increased Lp(a) atherogenicity in the context of HIV may be mediated, in part, by its role as being a preferential carrier of proinflammatory and proatherogenic OxPLs. Indeed, although data is lacking with regards to Lp(a)-OxPLs, HIV infection was associated with elevated levels of oxidized LDL, which were also correlated with biomarkers of monocyte activation.[33] Thus, further investigations directly assessing the roles of Lp(a)-OxPLs and/or post-ART residual inflammatory burden in mediating Lp(a)-associated elevated CVD risk in the setting of HIV are warranted.

In agreement with other studies, HIV was associated with a lower HDL-C and a higher triglyceride level.[19] However, TC and LDL-C levels were comparable across HIV status. Notably, in our cohort, none of these lipids and lipoproteins predicted cIMT in HIV-infected or HIV-uninfected women. In our cohort with a mean age of ~31 years, cIMT was lower in the HIV-infected vs. HIV-uninfected group. Consistent with these findings, a recent pooled analysis of five cohorts reported a lower cIMT value in the HIV-infected vs. HIV-uninfected group in the age range of 30–49 years (50% women in the HIV-infected group).[34]

Being a genetically regulated heritable trait, as opposed to traditional risk factors susceptible to lifestyle modifications or drug interventions, Lp(a) presents a unique setting where individuals with an elevated level and/or carriers of an atherogenic small size apo(a) are exposed to a high CVD burden over the entire course of their lifespan. Among HIV-infected individuals, the association of cIMT with traditional determinants of CVD burden, such as higher systolic BP or lower HDL-C, was strengthened with age.[34] This observation, together with our Lp(a) findings in young HIV-infected women, suggest that the effect of HIV on carotid artery structure may differ across the lifespan with HIV-specific mechanisms and/or novel factors [e.g., Lp(a)] may be playing a greater role in HIV-infected younger adults than in older adults. In a slightly older cohort of the WIHS (mean age: ~42 years), LDL-C and non-HDL-C levels were significantly and positively associated with cIMT in ART-treated HIV-infected women, but not in the untreated HIV-infected women.[35] Further, the significant association between these lipids and cIMT in the ART-treated HIV-infected women appeared to be weaker than those observed in the HIV-uninfected women.[35] Taken together, these findings indicate that the relationship of atherogenic and anti-atherogenic lipids with atherosclerotic processes in the HIV setting is a complex process and that the ability of these lipoproteins to predict cardiovascular risk may evolve over the course of HIV infection. Evidence further indicates that atherosclerotic processes start in early childhood progressing with age and that this process begins even prematurely among HIV-infected children and young adults.[36, 37]

Notably, the global impact of HIV disease and its treatment on Lp(a)-associated CVD risk may be substantial in that: 1) the majority of people with HIV live in sub-Saharan Africa and increasing numbers will be treated with antiretroviral treatment; 2) people of African ancestry have on average 2- to 3-times greater Lp(a) levels compared to those of non-African ancestry. Moreover, in the U.S., data also indicate that HIV infection

disproportionally affects ethnic minorities, in particular, young African-Americans. Collectively, these facts highlight the importance of Lp(a)/apo(a) to increase CVD risk in HIV-infected individuals in the era of HAART and open possibilities for a targeted intervention to reduce overall CVD risk in this vulnerable population.

We acknowledge some imitations of our study. First, our results are based on a cross-sectional assessment of the relationship between Lp(a) and cIMT in a women-only, relatively young HIV-infected cohort. Further longitudinal studies in HIV-infected women, as well as in HIV-infected men, and across the lifespan (children, adolescents, and older adults) are needed to confirm this relationship. Second, the cohort consisted of mainly African-Americans; there is a need to extend this observation to other racial/ethnic groups. Third, although we found a significant association between cIMT and Lp(a) in HIV-infected women on treatment, we were unable to address a possibility of differential impact by various treatment regimens. Fourth, although considered as a well-established indicator of future CVD risk, cIMT may not fully capture the complexity of HIV/HAART-induced deleterious effects on vascular structure. Studies with available data on carotid three dimensional imaging or carotid plaque volume determined by magnetic resonance imaging in HIV-infected populations may provide valuable information.

In conclusion, elevated levels of Lp(a) and/or allele-specific apo(a) carried by the smaller apo(a) sizes are associated with cIMT in HIV-infected young women. Further research is needed to identify underlying mechanisms of an increased Lp(a) atherogenicity in the setting of HIV infection. A disease biomarker that has the potential to remain informative over the course of lifespan due to its high heritability and relative resistance to interventions may support clinicians in their efforts to identifying HIV-infected individuals at increased risk for CVD, regardless of the stages of lifespan or HIV infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Data in this manuscript were collected by the Women's Interagency HIV Study (WIHS). The contents of this publication are solely the responsibility of the authors and do not represent the official views of the National Institutes of Health (NIH). WIHS (Principal Investigators): UAB-MS WIHS (Michael Saag, Mirjam-Colette Kempf, and Deborah Konkle-Parker), U01-AI-103401; Atlanta WIHS (Ighovwerha Ofotokun and Gina Wingood), U01-AI-103408; Bronx WIHS (Kathryn Anastos), U01-AI-035004; Brooklyn WIHS (Howard Minkoff and Deborah Gustafson), U01-AI-031834; Chicago WIHS (Mardge Cohen and Audrey French), U01-AI-034993; Metropolitan Washington WIHS (Seble Kassaye), U01-AI-034994; Miami WIHS (Margaret Fischl and Lisa Metsch), U01-AI-103397; UNC WIHS (Adaora Adimora), U01-AI-103390; Connie Wofsy Women's HIV Study, Northern California (Ruth Greenblatt, Bradley Aouizerat, and Phyllis Tien), U01-AI-034989; WIHS Data Management and Analysis Center (Stephen Gange and Elizabeth Golub), U01-AI-042590; Southern California WIHS (Joel Milam), U01-HD-032632 (WIHS I – WIHS IV).

Sources of Funding: The WIHS is funded primarily by the National Institute of Allergy and Infectious Diseases (NIAID), with additional co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the National Cancer Institute (NCI), the National Institute on Drug Abuse (NIDA), and the National Institute on Mental Health (NIMH). Targeted supplemental funding for specific projects is also provided by the National Institute of Dental and Craniofacial Research (NIDCR), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Deafness and other Communication Disorders (NIDCD), and the NIH Office of Research on Women's Health. WIHS data collection is also supported by UL1-TR000004 (UCSF CTSA) and UL1-TR000454 (Atlanta CTSA). The study was also supported by the NIH-

supported UCD Clinical and Translational Science Center base operating grant (TR001860), NIH K12 Building Interdisciplinary Research Career in Women's Health Program (NIH2K12HD051958) and R01 HL126543 NHLBI/NIH (Kaplan).

ABBREVIATIONS

Apo(a)	apolipoprotein(a)
ASL	allele-specific apo(a) level
ART	antiretroviral therapy
BMI	body mass index
BP	blood pressure
CHD	coronary heart disease
cIMT	carotid artery intima media thickness
CVD	cardiovascular disease
HAART	highly active antiretroviral therapy
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
K	Kringles
Lp(a)	lipoprotein(a)
LDL	low-density lipoprotein
RNA	ribonucleic acid
WIHS	Women's Interagency HIV Study

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HIGHLIGHTS

- HIV-related elevated cardiovascular risk cannot be fully explained by traditional risk factors.
- Lp(a) and allele-specific apo(a) levels predicted cIMT in an HIV-infected young predominantly African-American women cohort.
- The association remained significant after a multivariate adjustment for covariates.
- The significant association was seen only in the treated HIV-infected women.
- Further research is needed to identify underlying mechanisms of an increased Lp(a) atherogenicity in HIV.

Table 1

Characteristics of study population

	HIV-uninfected (N=100)	HIV-infected			*P*-value between HIV-uninfected vs. HIV-infected All	*P*-value between HIV-infected Untreated vs. HIV-infected Treated
		All (N=150)	Untreated (N=74)	Treated* (N=76)		
Age (years)	30.4 ± 4.0	30.7 ± 3.9	29.9 ± 4.1	31.4 ± 3.6	0.612	0.027
Race, n (%)					0.640	0.683
White (non-Hispanic)	4 (4%)	9 (6%)	4 (5%)	5 (7%)		
White (Hispanic)	13 (13%)	18 (12%)	7 (9%)	11 (14%)		
African-American (Non-Hispanic)	72 (72%)	99 (66%)	52 (70%)	47 (62%)		
African-American (Hispanic)	4 (4%)	5 (3%)	3 (4%)	2 (3%)		
Other (Hispanic)	6 (6%)	18 (12%)	7 (9%)	11 (14%)		
Asian/Pacific Islander	1 (1%)	1 (1%)	1 (1%)	0 (0%)		
Body mass index (kg/m^2)	32 ± 10	29 ± 7	31 ± 8	27 ± 7	0.045	0.003
Systolic BP (mmHg)	115 ± 15	115 ± 13	116 ± 14	114 ± 11	0.833	0.334
Diastolic BP (mmHg)	67 ± 11	69 ± 10	70 ± 10	68 ± 10	0.029	0.330
CD4+ T cell count (cells/mm^3)					<0.0001	0.551
<200	0 (0%)	18 (12%)	10 (14%)	8 (11%)		
200–349	0 (0%)	38 (25%)	19 (26%)	19 (25%)		
350–499	2 (2%)	32 (21%)	15 (20%)	17 (22%)		
≥500	78 (78%)	60 (40%)	28 (38%)	32 (42%)		
Missing	20 (20%)	2 (1%)	2 (3%)	0 (0%)		
HIV RNA (copies/mL)	N/A				N/A	<0.0001
≤80 (lower detection limit)		59 (39%)	10 (14%)	49 (64%)		
81–999		22 (15%)	10 (14%)	12 (16%)		
1000–9999		27 (18%)	23 (31%)	4 (5%)		
≥10000		42 (28%)	31 (42%)	11 (14%)		
Heart or BP medication, n (%)	3 (3%)	6 (4%)	2 (3%)	4 (5%)	0.745	0.681
Diabetic medication, n (%)	3 (3%)	3 (2%)	1 (1%)	2 (3%)	0.686	1.000
Current smoker, n (%)	33 (33%)	61 (41%)	32 (43%)	29 (38%)	0.233	0.618

	HIV-uninfected (N=100)	HIV-infected			*P*-value between HIV-uninfected vs. HIV-infected All	*P*-value between HIV-infected Untreated vs. HIV-infected Treated
		All (N=150)	Untreated (N=74)	Treated* (N=76)		
HCV co-infection, negative, n (%)	97 (97%)	144 (96%)	71 (96%)	73 (96%)	0.858	0.838
cIMT (μm)	670 ± 80	645 ± 70	640 ± 66	651 ± 73	0.014	0.351
Total cholesterol (mg/dL)	169 ± 36	166 ± 36	157 ± 29	174 ± 41	0.454	0.005
LDL cholesterol (mg/dL)	98 ± 33	98 ± 33	98 ± 30	97 ± 36	0.944	0.719
HDL cholesterol (mg/dL)	53 ± 13	45 ± 18	38 ± 14	51 ± 18	<0.0001	<0.0001
Non-HDL cholesterol (mg/dL)	116 ± 38	121 ± 35	119 ± 30	123 ± 39	0.164	0.769
Triglycerides (mg/dL)	75 (54, 101)	106 (70, 140)	97 (66, 126)	109 (73, 152)	<0.0001	0.085
Insulin (μlU/mL)	10.7 ± 6.3	13.4 ± 9.2	12.7 ± 7.9	14.1 ± 10.4	0.032	0.838
Glucose (mg/dL)	85 ± 20	88 ± 25	88 ± 29	87 ± 20	0.101	0.827

Data are presented as mean ± standard deviation or number (%), except for triglycerides which are given with median (interquartile range).

*: The treated HIV+ group included 73 subjects on HAART, 2 subjects on combination therapy and 1 subject on monotherapy.

Abbreviations: BP, blood pressure; cIMT, carotid intima media thickness; HCV, hepatitis C virus; HDL, high-density lipoprotein; LDL, low-density lipoprotein;

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Table 2

Characetristics of Lp(a) and apo(a)-related variables

	HIV-uninfected	HIV-infected			*P*-value between HIV-uninfected vs. HIV-infected All	*P*-value between HIV-infected Untreated vs. HIV-infected Treated
		All	Untreated	Treated		
Plasma level:						
Lp(a) (mg/dL)	25 (12, 54)	19 (9, 38)	20 (12, 38)	15 (5, 38)	0.024	0.133
Prevalence of high Lp(a)						
≥30 mg/dL, n (%)	43 (43%)	48 (32%)	25 (34%)	23 (30%)	0.083	0.727
median (IQR), mg/dL	61 (41, 85)	51 (39, 68)	46 (38, 66)	57 (41, 76)	0.301	0.361
≥50 mg/dL, n (%)	27 (27%)	25 (17%)	11 (15%)	14 (18%)	0.057	0.663
median (IQR), mg/dL	75 (61, 91)	68 (62, 87)	67 (63, 78)	68 (61, 91)	0.532	1.000
ASL, larger (mg/dL)	7 (2, 18)	6 (3, 14)	8 (3, 16)	5 (2, 12)	0.571	0.381
ASL, smaller (mg/dL)	19 (8; 37)	14 (6; 27)	14 (8; 25)	10 (3; 35)	0.037	0.187
Apo(a) isoform size:						
Apo(a), larger (K)	31 (29, 33)	31 (29, 33)	31 (28, 33)	32 (30, 34)	0.656	0.117
Apo(a), smaller (K)	27 (23, 28)	26 (23, 28)	25 (23, 27)	27 (24, 30)	0.474	0.026
Prevalence of small apo(a) (≤22K), n (%)	18 (18%)	27 (18%)	16 (22%)	11 (14%)	0.497	0.430
Apo(a) expression:					0.490	0.394
Single isoform, n (%)	26 (26%)	40 (27%)	16 (22%)	24 (32%)		
Double isoforms, n (%)	74 (74%)	107 (71%)	56 (76%)	51 (67%)		
No isoform, n (%)	0 (0%)	3 (2%)	2 (3%)	1 (1%)		
Apo(a) dominance (double bands only):					0.657	0.860
Smaller-dominating, n (%)	38 (51%)	50 (47%)	26 (46%)	24 (47%)		
Larger-dominating, n (%)	6 (8%)	13 (12%)	6 (11%)	7 (14%)		
Co-dominating, n (%)	30 (41%)	44 (41%)	24 (43%)	20 (39%)		

Data are presented as median (IQR) or number (%).

Abbreviations: Apo(a), apolipoprotein(a); ASL, allele-specific apo(a) level; K, Kringle; IQR, interquartile range; Lp(a), Lipoprotein(a)

Table 3

Correlations of carotid intima media thickness with clinical variables

	HIV-uninfected		HIV-infected					
			All		Untreated		Treated	
	β (95% CI)	*p*-value*	β (95% CI)	*p*-value*	β (95% CI)	*p*-value*	β (95% CI)	*p*-value*
Age (years)	0.00801 (0.00433,0.01169)	<0.0001	0.00487 (0.00210,0.00764)	0.0007	0.00452 (0.00074,0.00831)	0.020	0.00514 (0.00082,0.00941)	0.020
Systolic BP (mmHg)	0.00193 (0.00094,0.00293)	0.0002	0.00070 (−0.00020,0.00159)	0.127	0.00059 (−0.00060,0.00178)	0.327	0.00095 (−0.00043,0.00233)	0.179
Diastolic BP (mmHg)	0.00144 (−0.00005,0.00292)	0.057	−0.00021 (−0.00137,0.00094)	0.719	0.00049 (−0.00114,0.00212)	0.551	−0.00084 (−0.00248,0.00080)	0.318
BMI (kg/m^2)	0.00148 (−0.00012,0.00308)	0.069	0.00135 (−0.00018,0.00288)	0.083	0.00113 (−0.00099,0.00325)	0.295	0.00208 (−0.00022,0.00439)	0.079
Current smoking	0.05835 (0.02651,0.09020)	0.0004	0.01499 (−0.00783,0.03781)	0.196	0.03706 (0.00513,0.069)	0.023	−0.00616 (−0.03803,0.02571)	0.706
Viral load (copies/mL)	N/A	N/A	−0.00263 (−0.00678,0.00152)	0.212	−0.00298 (−0.00982,0.00387)	0.392	−0.00141 (−0.00833,0.00551)	0.691
CD4+ T-cell (cells/mm^3)	0.02116 (−0.03394,0.07627)	0.447	0.01622 (0.00130,0.03113)	0.033	0.01482 (−0.00802,0.03765)	0.202	0.01731 (−0.00232,0.01963)	0.086
TC (mg/dL)	0.00033 (−0.00011,0.00077)	0.135	−0.00001 (−0.00032,0.00031)	0.976	−0.00024 (−0.00081,0.00033)	0.411	0.00004 (−0.00035,0.00043)	0.832
LDL-C (mg/dL)	0.00041 (−0.00007,0.00089)	0.095	−0.00007 (−0.00042,0.00027)	0.674	−0.00015 (−0.00071,0.00040)	0.581	−0.00002 (−0.00046,0.00042)	0.939
HDL-C (mg/dL)	−0.00093 (−0.00213,0.00028)	0.130	0.00007 (−0.00058,0.00071)	0.835	−0.00063 (−0.00178,0.00053)	0.285	0.00026 (−0.00060,0.00112)	0.550
Non-HDL-C (mg/dL)	0.00041 (−0.00001,0.00083)	0.051	−0.00005 (−0.00038,0.00028)	0.768	−0.00013 (−0.00068,0.00041)	0.625	−0.00001 (−0.00042,0.00040)	0.952
TG (mg/dL)	0.00904 (−0.02406,0.04214)	0.589	0.00552 (−0.01640,0.02743)	0.620	0.01139 (−0.02224,0.04502)	0.504	−0.00217 (−0.03155,0.02721)	0.885
Glucose (mg/dL)	0.00131 (0.00050,0.00211)	0.002	0.00033 (−0.00013,0.00079)	0.154	0.00041 (−0.00015,0.00097)	0.152	0.00018 (−0.00063,0.00098)	0.664
Insulin (μlU/mL)	0.00257 (−0.00002,0.00517)	0.052	−0.00047 (−0.00172,0.00078)	0.460	−0.00082 (−0.00286,0.00121)	0.426	−0.00028 (−0.00188,0.00132)	0.731

Abbreviations: BP, blood pressure; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides;

*: A *p*-value less than 0.05 indicates a significant correlation of cIMT with the variable within the group. Conversely, a *p*-value greater than 0.05 for a variable indicates that there is no significant correlation of that variable with cIMT within the group.

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Table 4

Correlations of Lp(a) and allele-specific apo(a) levels with carotid intima media thickness before and after adjustments for covariates*

	HIV-uninfected		HIV-infected					
			All		Untreated		Treated	
	β (95% CI)	*p-value*†	β (95% CI)	*p-value*†	β (95% CI)	*p-value*†	β (95% CI)	*p-value*†
Before adjustment:								
Lp(a) (mg/dL)	0.00175 (−0.00458,0.00809)	0.584	0.00542 (0.00057,0.01026)	0.029	0.00247 (−0.00526,0.01021)	0.528	0.00775 (0.00156,0.01392)	0.015
ASL, larger (mg/dL)	0.00057 (−0.00047,0.00160)	0.279	0.00096 (−0.00022,0.00215)	0.110	0.00043 (−0.00117,0.00202)	0.599	0.00173 (−0.00001,0.00346)	0.054
ASL, smaller (mg/dL)	0.00021 (−0.00049,0.00091)	0.558	0.00074 (0.00011,0.00138)	0.022	0.00045 (−0.00061,0.00151)	0.400	0.00091 (0.00012,0.00170)	0.025
After adjustment:								
Lp(a) (mg/dL)	0.00004 (−0.00662,0.00670)	0.991	0.00563 (0.00042,0.01085)	0.035	0.00323 (−0.00543,0.01189)	0.462	0.00696 (0.00054,0.01338)	0.036
ASL, larger (mg/dL)	0.00088 (−0.00021,0.00197)	0.110	0.00089 (−0.00034,0.00213)	0.153	0.00014 (−0.00154,0.00182)	0.870	0.00172 (−0.00001,0.00345)	0.055
ASL, smaller (mg/dL)	−0.00003 (−0.00071,0.00064)	0.920	0.00088 (0.00022,0.00154)	0.010	0.00065 (−0.00044,0.00174)	0.238	0.00101 (0.00019,0.00183)	0.018

*: Model adjusted for age, race, current smoker, hepatitis C virus, BMI, systolic and diastolic blood pressure, LDL cholesterol, HDL cholesterol, triglycerides, HIV RNA viral load, CD4+ T-cell count and menopausal status.

Abbreviations: ASL, allele-specific apo(a) level; Lp(a), lipoprotein(a)

†: A *p*-value less than 0.05 indicates a significant correlation of Lp(a) or ASL with cIMT within the respective group. Conversely, a *p*-value greater than 0.05 indicates that there is no significant correlation of Lp(a) or ASL with carotid intima media thickness within the group.