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Lipid Abnormalities and Inflammation in HIV infection

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Abstract

Infection with the human immunodeficiency virus (HIV), and subsequent treatment with antiretroviral therapy (ART), is often associated with perturbations in lipid profiles. Furthermore, persistent inflammation, in spite of suppression of viral replication by ART, likely contributes to modifications in lipid composition and function, exacerbating risk for development of cardiovascular disease (CVD). Increased levels of several pro-inflammatory lipid species, including oxidized LDL and HDL, have been measured in HIV-infected persons and are associated with markers of immune activation. The mechanisms linked to this bidirectional relationship in which inflammation increases lipid levels and promotes their modification, and these modified lipid species perpetuate inflammatory processes, require further investigation. Treatment with statins and other lifestyle modifications, including improvement in dietary intake and exercise, are critical to reducing CVD risk. Well-designed clinical trials that take into account the complex relationships among lipids and inflammation within persons infected with HIV need to be considered.

Keywords

antiretroviral therapy; inflammation; lipid composition; oxidized LDL; statins; HDL cholesterol efflux

Introduction

Human immunodeficiency virus (HIV) infection[1], its treatment[2], and chronic inflammation[3] can all alter lipid and metabolic profiles[4, 5]. Advances in the effectiveness and availability of modern antiretroviral therapy (ART) combinations has

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Compliance with Ethics Guidelines

Conflict of Interest

Nehal N. Mehta declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

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prolonged the lives of persons living with HIV, but these patients are at an increased risk of cardiovascular disease (CVD) with CVD events occurring at younger ages for this population[6]. Careful monitoring and treatment of lipid levels, and measurement of emerging particle subclasses and function, are likely more informative in persons infected with HIV than among persons who are not infected, due to the complex and multidirectional relationships among diet, genetic factors, ART, viral replication, chronic inflammation, and lipid metabolism (Figure 1).

HIV infection and ART alter lipid profiles by traditional lipid measurement, decreasing HDL and increasing LDL and Triglycerides

Infection with HIV[1] and subsequent treatment with antiretroviral therapy[2, 7, 8] has been associated with changes in lipid concentrations, including decreased levels of high density lipoprotein (HDL) cholesterol and increased levels of low density lipoprotein (LDL) cholesterol, total cholesterol (TC) and triglycerides. Environmental factors including diet, genetic factors, and ART-induced adipose tissue dysfunction and dyslipidemia, all likely contribute to metabolic disease in chronic HIV infection[2]. The altered lipid profiles associated with chronic ART-treated HIV infection may, in part, explain the increased risk of cardiovascular disease (CVD) events that has been reported for HIV+ persons, compared to uninfected controls [4, 9]. The metabolic effects of specific combinations of ART have been extensively reviewed[2, 10]. In brief, modern ART regimens, that often include integrase inhibitors, are more “lipid friendly” than older drug combinations that rely more heavily on protease inhibitors (PI) and certain nucleoside reverse transcriptase inhibitors (NRTIs)[2, 9], and may have fewer adverse cardiovascular complications[11]. Yet, even among HIV+ persons receiving regimens that are not known to adversely modulate lipid profiles, alterations in lipid concentration and composition are often observed[2].

Traditional lipid panels may not adequately assess lipid changes and CVD risk in HIV infection

While traditional lipid measurements of concentration (total HDL, LDL, and triglycerides) are performed routinely in the clinic, altered lipoprotein species and lipid particle sizes are closer correlates of cardiovascular disease risk than these commonly measured lipid fractions in both HIV-1 infected[12, 13] and uninfected populations[14, 15]. Lipoprotein subclass profiles change following initiation of ART[13, 16] and during treatment interruption[17]. Patients undergoing antiretroviral treatment interruption, compared to those undergoing continuous therapy, demonstrate significant decreases in total, large, and TG concentrations, but due to concurrent decreases in HDL particle concentrations, the overall lipid profile remained atherogenic within these individuals[17]. Further, in patients switching from a PI-based ART regimen, to one using an integrase inhibitor, significant improvements in the lipid profiles of these patients (i.e decreased LDL, TC, TG, and an increase in the apolipoprotein A1/apolipoprotein B (ApoA1/ApoB ratio) has been reported[16].

In addition to measurement of ApoA1 and ApoB, emerging NMR spectroscopic studies[18, 19] have demonstrated a close relationship between HDL particle size and HDL function, measured by HDL cholesterol efflux capacity (CEC). CEC permits understanding of how

HDL derived from a patient sample performs reverse cholesterol transport, a process whereby cholesterol from peripheral tissues is removed from the body, excreted in the bile. This CEC can be measured reliably using patient serum and a validated assay, however, CEC remains only for research purposes. The potential prognostic clinical value of CEC is growing; CEC has been related to future CV events [20], CVD by coronary angiography [18], as well as to non-calcified plaque burden[21] in non-HIV patients. Among HIV-infected persons with “normal” lipid profiles based on traditional measures, an increase in LDL particle number, and a decrease in large HDL particles and reduced CEC, suggesting that traditional lipid panels may not adequately describe the atherogenic potential of lipid profiles in HIV infection[22].

Until recently, the dynamic changes in lipid profile composition, HDL function, and inflammatory biomarker levels have not been adequately described following ART initiation. In a substudy of the AIDS Clinical Trials Group (ACTG) A5248 Study[23, 24], authors examined complex lipid phenotypes, including lipid particle number and size, and HDL function by HDL efflux capacity, longitudinally following ART initiation using a raltegravir (RAL)-based regimen. RAL is an HIV-1 integrase inhibitor that is thought to be relatively “lipid-neutral.” Participants initiating RAL had rapid reductions in viremia[23] without normalization of plasma levels of inflammation[24]. Significant increases in TC (13mg/dL; $p<0.001$), LDL (8mg/dL; $p=0.03$), and HDL (7mg/dL; $p<0.001$) were seen following 48 weeks of ART. The HDL increase was accompanied by increases in HDL particle number (4 $\mu\text{mol/L}$; $p<0.001$) and HDL efflux (7% increase; $p<0.001$), but these beneficial HDL changes did not reach levels measured in a demographically matched HIV– group [25]. Retrospective studies among HIV+ donors who experienced a CVD event, that measure cholesterol particle size, concentration, and function, may provide an incremental increase in the ability of clinicians to identify HIV+ persons at risk for a CVD event.

Chronic inflammation in HIV infection: Cause or consequence of Altered Lipid Profiles?

Alterations in lipid profiles among HIV+ persons are complicated further by the persistent inflammation and immune activation that are often reported in HIV infection, even when viral replication is suppressed by ART [26, 27]. While combination ART increases dramatically the expected lifespan of HIV-infected persons, cardiovascular disease risk is increased in this population[28-32]. Increased immune activation in HIV infection likely contributes to increased venous and arterial thromboses[6-8, 33-41] and may be a cause or consequence of altered lipid profiles. The Strategies for Management of Anti-Retroviral Therapy (SMART) study found that plasma levels of interleukin-6 (IL-6), C-reactive protein (hsCRP), and D-dimer products of fibrinolysis are independent predictors of mortality, including deaths related to CVD, in HIV infection[42, 43]. The SMART study also demonstrated that total, large, and small HDL particles, but not very low density LDL (VLDL) or LDL particles, were associated with risk for CVD events, and that there was an inverse relationship between HDL particle numbers and IL-6 and D-dimer levels[13]. Piconi et al have also reported that LDL and ApoA1 are better correlates of CVD risk in ART-treated, HIV+ persons than are inflammatory markers (CRP, TNF- α)[44]; yet, it is difficult to separate the affects lipid profiles and inflammation on CVD-risk, as they are closely linked.

Inflammation modulates lipid particles and lipid transport

Lipids are important in CVD associated with HIV infection, and persistent inflammation may also be critical, or even synergistic, in CVD risk via lipid mediated pathways. Levels of inflammatory markers (IL-6 and hsCRP) before initiation of ART are inversely related to improvements in HDL particle number and ApoA1 following 6 months of ART [45]. Chronic inflammatory conditions, including systemic lupus erythematosus, rheumatoid arthritis[46], and psoriasis[47], much like HIV infection, have been associated with increases in atherogenic lipid profiles and decreases in HDL levels and function. Several mechanisms for modulating cholesterol homeostasis in the blood compartment and within the walls of blood vessels are closely regulated by inflammation and the acute phase response[3, 48]. Reverse cholesterol transport (RCT), where HDL removes atherogenic lipid molecules from atherosclerotic plaques for clearance by the liver[49] is impaired by inflammation[48]. Macrophages within the vascular wall shuttle atherogenic lipid molecules onto HDL or ApoA1 for reverse cholesterol efflux through a number of ATP-binding cassette transporters (ABC transporters), initiating RCT, and leading to cholesterol excretion[50, 51]. Exposure to Toll-like receptor ligands (TLRs), including lipopolysaccharide (LPS) can modulate expression of ABC transporters and reduce efficiency of reverse cholesterol transport[48]. This may be of particular importance in HIV-infection, as plasma levels of LPS and other microbial products, are increased in HIV-infected persons as a result of microbial translocation[52-55]. Maisa et al recently reported that monocytes exposed to pooled-serum from ART-treated persons infected with HIV more readily become foam cells than cells exposed to pooled serum from HIV- donors, and that monocytes from HIV+ donors also had lower levels of *ABCA1* gene expression[56], suggesting that both monocyte and HDL function may contribute to decreased cholesterol efflux in HIV infection, likely driven by chronic immune activation.

Inflammation and oxidative modulation of lipids

Chronic innate immune activation in ART-treated HIV infection[26] may promote increases in LDL levels by altering how lipids are processed and transported, and immune activation likely enhances modification of these increased lipid molecules through the activity of reactive oxygen species (ROS) or enzymes such as lipoprotein-associated phospholipase A2 (Lp-PLA₂)[57], rendering them more “inflammatory.” Modified lipid species, including oxidized forms of LDL (oxLDL)[58, 59] and HDL (HDL_{ox}) [60, 61], may contribute directly to monocyte[62] and endothelial cell activation in HIV disease, placing them on the mechanistic pathway for increased inflammation, immune activation, and CVD risk. Results from the ACTG substudy A5260s demonstrate that levels oxidized HDL are related to markers of inflammation and immune activation at baseline (IL-6, hsCRP, %CD38+HLA-DR+CD8+ T cells, sCD163) and following 96 weeks of ART (markers as before, including sCD14) [63]. Oxidized HDL can induce cellular activation through the scavenger receptor CD36 on monocytes/macrophages[61].

OxLDL levels are increased in HIV-infection[62], confirming a previous report[64]. Also, in HIV+ individuals, levels of oxLDL, but not LDL, were related to sCD14 and the proportion of CD14+CD16+ “inflammatory” monocytes that express tissue factor (TF)[62]. In a separate study, initiation of ART resulted in decreases in oxLDL levels by week 12 (p=0.02),

but these levels rose subsequently, concurrent with LDL increases; interestingly, sCD14 levels also fell rapidly, plateaued by week 24, but rose between weeks 24 and 48 [25]. Oxidized LDL can activate monocytes and endothelial cells through interactions with the lectin-like oxidized low-density lipoprotein receptor-1 (Lox-1)[65-67] or the heterotrimer of CD36/TLR4/TLR6[58, 59, 68] increasing expression of adhesion molecules[65, 68], chemokines, and cytokines[58, 59]. Monocytes from HIV+ individuals exposed to oxLDL resulted in greater production of IL-1 β than did oxLDL stimulated cells from uninfected donors[69]. Primary blood monocytes increase TF expression in response to oxLDL[68], which may contribute to activation of the extrinsic coagulation cascade and increases in D-dimer levels[70, 71].

Oxidized LDL induced activation of monocytes and macrophages may be an important contributor of blood vessel inflammation in HIV infection, as markers of monocyte/macrophage activation (sCD14 and sCD163) have been linked to oxLDL levels[62], coronary calcium[72], mortality[73, 74], and with non-calcified coronary artery plaques [75], with perivascular fat[76], and with arterial inflammation in HIV-infected subjects[77]. Macrophage induced vascular inflammation may be generated, in part, by the activity of Lp-PLA₂[57], an enzyme produced by macrophages that can cleave oxLDL into lysophosphatidylcholine (LPC) and oxidized-free fatty acids (oxFA). Levels of Lp-PLA₂ are related to both oxLDL levels and carotid atherosclerosis[78], and risk for coronary heart disease in HIV-uninfected individuals[79]. A relationship between oxLDL levels and carotid intima-media thickness (cIMT) in HIV+ persons has been reported [80]. Levels of oxLDL in carotid plaques from HIV- donors are directly related to macrophage infiltration, and plaque oxLDL levels can be 70 times greater than levels in circulation[81]. Modulation of pro-inflammatory lipid levels and myeloid cell activation are targets for therapeutic intervention in chronic HIV infection.

Inflammation and lipid subclass by lipidomics

Oxidized forms of HDL and LDL provide “model” pro-inflammatory lipids that can be measured for a gross estimate of lipids that may contribute to inflammation in HIV infection. Several lipid subclasses are pro-inflammatory and contribute to CVD in the general population[82-84]. Cholesterol crystals, a potential byproduct of inefficient RCT, can activate macrophages, inducing inflammasome activation and production of IL-1 β [85], a cytokine that is associated ischemic heart disease[86]. Advances in liquid chromatography electrospray ionization tandem mass spectrometry (LC ESI- MS/ MS), can provide information on the biosynthesis and metabolism of over 1,000 individual lipid species, many of which can modulate inflammation[87, 88]. Recently, Wong et al measured the lipidome of 113 donors, including an HIV uninfected group, and a subgroup of HIV+ donors with samples available within 1 year of CVD diagnosis[89]. Eighty-three individual lipid species, among several lipid classes, were associated with HIV infection, including: ceramides (Cer), phosphatidylcholine (PC), and several species of diacy- and triacylglycerols (DG and TG). Further analyses described an association among DGs, TGs, Cer, and cholesterol esters, with risk for CVD in HIV+ individuals. Similar lipid profiles are related to CVD risk[90], including non-calcified coronary plaque[91, 92] and diabetes[93] in HIV- donors. Many of these lipid species have pro-inflammatory properties. Ceramides induce NF κ B and pro-

inflammatory cytokines in mice[94] and are related to mortality in chronic heart failure in humans[95]. Several lipid species not reported by the Wong study, including eicosanoids, molecules derived from oxidation of ω -3 and ω -6, are involved in pro-inflammatory signaling[96], and their levels should be assessed samples from HIV+ and well-matched HIV- donors. Currently, high resolution longitudinal analyses of changes in lipid species among persons infected with HIV have not been reported and deserve consideration.

Lipid lowering therapies, especially statins, are an important secondary treatment strategy in ART+ HIV+ patients

Perturbations in lipid profiles and the increased risk for CVD reported in chronic HIV infection[1, 4, 6-8, 97] has generated significant interest in modulating lipid levels and inflammation in HIV+ persons, especially though the use of statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors)[98]. The effects of statin use among HIV infected individuals has recently been reviewed[99], and overall, statin use was well-tolerated and improved lipid profiles. Recently, two double blind, placebo controlled trials among HIV-infected participants (with LDL cholesterol<130mg/dL) have demonstrated significant beneficial effects on markers of inflammation and CVD risk[100-103]. Nou et al report that significant reductions in non-calcified plaque volumes were measured by coronary CT angiography among HIV+ participants receiving atorvastatin[103]. The Stopping Atherosclerosis and Treating Unhealthy Bone with Rosuvastatin in HIV (SATURN-HIV) randomized 147 HIV+ ART+ participants with normal LDL (<130mg/dL), but with elevated markers of inflammation/immune activation (hsCRP>2.0mg/dL or CD8+CD38+HLA-DR+ 19%) to treatment with 10mg of rosuvastatin or placebo, and changes in several biomarkers of CVD risk and immune activation were measured over 96 weeks. Results from SATURN HIV also demonstrated, for the first time in ART-treated subjects, that rosuvastatin treatment reduced levels of T-cell and monocyte activation markers[101, 102], including reduction in monocyte tissue factor expression, and sCD14, a marker of monocyte activation linked to morbidity in HIV+ patients[73, 74]. This study also showed that statin therapy reduced vascular inflammation[100, 101] and markers of cardiac strain, and may preserve renal function in ART-treated HIV+ subjects[104].

Both studies also report that statin use reduces levels of Lp-PLA₂ and oxLDL[100, 101, 103, 105]. Atorvastatin use decreased oxLDL levels, and this change was associated with a reduction in non-calcified plaque volume; independent of viremia, CD4 count or LDL levels[103]. Hileman et al report that rosuvastatin treatment induced changes in oxLDL were directly related to decreases in sCD14 and TF expression on patrolling monocytes (CD14^{Dim} CD16+), and improvements in cIMT[105]. The association between changes in oxLDL levels and improvements in cIMT remained after adjusting for other known risk factors including age, sex, race, smoking, BMI, HOMA-IR, Hepatitis C status, nadir CD4+ cell count, and PI use, placing oxLDL on the causal pathway of CVD progression in HIV-infection[105]. Statin pre-treatment also maintained the expression levels of the anti-inflammatory transcriptional regulator, Kruppel-like Factor 2 (KLF-2) in an aortic endothelial cell line exposed to oxLDL in vitro; potentially providing another link to statin use and improvement in vascular inflammation and function[106]. These results add to the growing interest in the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE,

NCT02344290); where 6,500 HIV infected participants will be randomized to pitavastatin or placebo, and will be followed for clinical endpoints. Modulation of lipid composition and function by other methods should also be considered. Recently, sevelamar, a phosphate lowering drug, lowered LDL, oxLDL, and soluble TF levels in HIV-infected participants [107]. Studies that explore the beneficial effects of exercise and dietary interventions in dyslipidemic ART+ participants, with a focus on changes in the microbiome, lipidome, and inflammatory markers, should also be explored further.

Conclusion

HIV is associated with primary and treatment associated lipid disturbances. Furthermore, persistent inflammation in treated HIV patients contributes to modifications of lipid composition and function, further potentially exacerbating CVD. Treatment with statins and other lifestyle modifications are critical to mitigate CVD risk, but the optimal strategies remain to be determined with ongoing clinical trials.

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Figure 1. Infection with HIV, and subsequent treatment with ART, is often associated with perturbations in lipid levels

Alterations in lipid profiles among HIV+ persons are complicated further by the bidirectional relationships among lipid metabolism and transport and persistent inflammation and immune activation. The effects of lipid lowering agents, including statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors), on lipid profiles and levels of chronic inflammation are currently being explored in persons living with HIV. {AU Query: Please add source of Figure 1 if not original.}