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HIV PATHOGENESIS AND TREATMENT (AL LANDAY AND NS UTAY, SECTION EDITORS)

Lipidome Abnormalities and Cardiovascular Disease Risk in HIV Infection

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Abstract

Purpose of Review Human immunodeficiency virus (HIV) infection and its treatment with antiretroviral therapy (ART) are associated with lipid abnormalities that may enhance cardiovascular disease risk (CVD).

Recent Findings Chronic inflammation persists in HIV+ individuals, and complex relationships exist among lipids and inflammation, as immune activation may be both a cause and a consequence of lipid abnormalities in HIV infection. Advances in mass spectrometry-based techniques now allow for detailed measurements of individual lipid species; improved lipid measurement might better evaluate CVD risk compared with the prognostic value of traditional assessments.

Summary Lipidomic analyses have begun to characterize dynamic changes in lipid composition during HIV infection and following treatment with ART, and further investigation may identify novel lipid biomarkers predictive of adverse outcomes. Developing strategies to improve management of comorbidities in the HIV+ population is important, and statin therapy and lifestyle modifications, including diet and exercise, may help to improve lipid levels and mitigate CVD risk.

Keywords Lipidome · Free fatty acids · HIV · Cardiovascular disease · Inflammation

Introduction

Antiretroviral therapy (ART) has prolonged the lives of individuals living with HIV; however, morbidity and mortality rates remain elevated compared with the general population. Management of comorbidities has become increasingly important in individuals chronically infected with HIV. HIV-infected (HIV+) individuals are at increased risk for cardiovascular disease (CVD), which persists despite virologic suppression with ART [1, 2•]. Further, HIV infection [3], ART [4], and chronic immune activation [5] can all alter lipid and metabolic profiles [6, 7]. Thus, monitoring and controlling lipid levels are crucial for HIV+ individuals, likely even more so than for the HIV-uninfected population. Modern mass spectrometry-based techniques enable comprehensive lipid analyses in which concentration and composition of individual lipid species can be evaluated (the lipidome). This review focuses on the effects of HIV infection and its treatment, on the lipidome, and the relationships among lipid abnormalities and enhanced CVD risk in HIV+ individuals (Fig. 1).

HIV Infection and ART Treatment Both Alter Traditional Lipid Measurements

Lipids have diverse biological roles, including signal transduction, protein trafficking, and regulation of membrane permeability [8]. The physiological importance of lipids is underscored by the numerous diseases associated with lipid abnormalities, including CVD, diabetes, obesity, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), and Alzheimer's disease [9–14]. Dyslipidemia is often observed in HIV+ individuals and is associated with reduced levels of high-density (HDL) cholesterol and increased low-density (LDL) lipoprotein, total (TC) cholesterol, and triglycerides (TG) [3]. Similar lipid profiles have been linked to the development of atherosclerosis in the general population [15].

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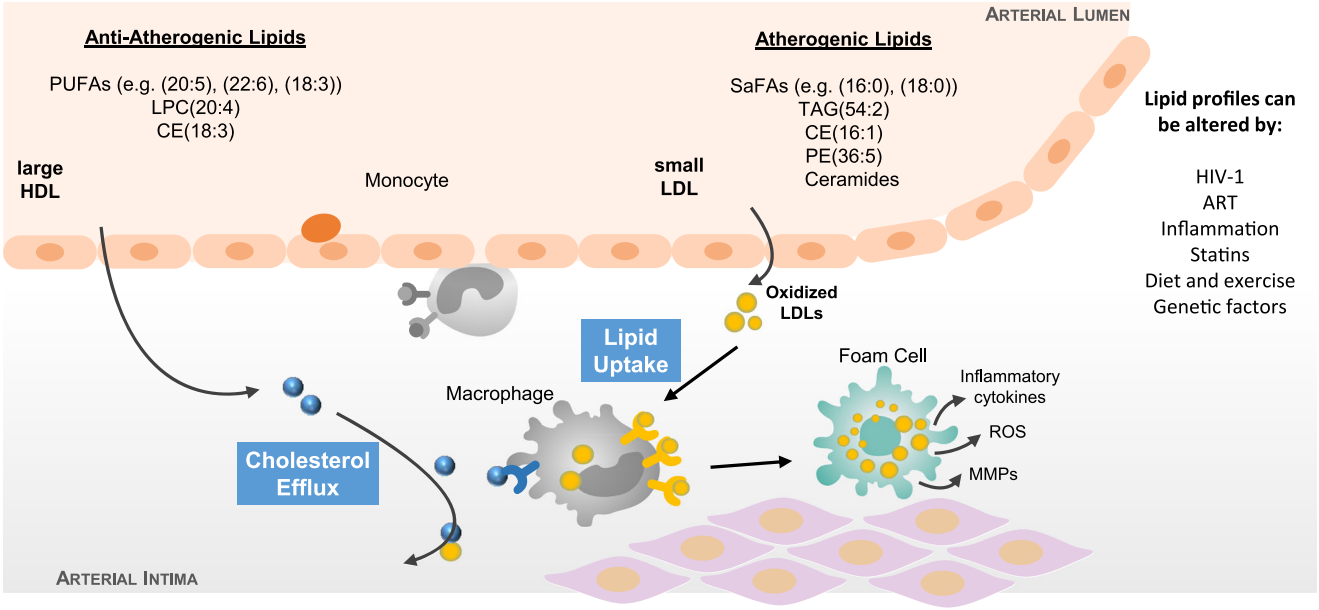

Fig. 1 Lipid abnormalities and enhanced CVD risk in HIV+ individuals may be driven by HIV itself, its treatment with ART, or the immunologic consequences associated with chronic HIV-infection

HIV-associated dyslipidemia was observed prior to the advent of ART [3]; however, specific combinations of ART drugs also have varying effects on lipid metabolism [4, 16], likely contributing to increased risk of CVD [17]. ART-associated lipid abnormalities are most evident with protease inhibitor (PI) use, particularly when combined with inhibitors of cytochrome p450 3A4, but other drug classes, including nucleoside reverse transcriptase inhibitors (NRTIs), may also have deleterious effects [17, 18]. Even with the most "lipid friendly" ART regimens, alterations in lipid concentration and composition are frequently observed [4].

Interventions to increase HDL concentrations in humans have failed to reduce clinical cardiovascular events, suggesting that overall HDL levels are not always reflective of efficient function [19–21]. HDL has several cardioprotective and anti-inflammatory roles, including promoting cholesterol efflux from macrophages in the vessel wall via reverse cholesterol transport, preventing oxidative modification of LDL, and supporting endothelial cell repair [22–25]. Importantly, the cholesterol efflux capacity of HDL particles was shown to be inversely related to CVD risk, and this was independent of total HDL concentration [26]. The anti-atherogenic function of HDL is often compromised during HIV infection and in inflammatory environments [27, 28]. Exposure to Toll-like receptor (TLR) ligands, such as lipopolysaccharide (LPS), can impair the efficacy of reverse cholesterol transport [29]. This is particularly significant in HIV infection, as reduced gut barrier function and increased plasma levels of microbial products have been reported in HIV+ individuals [30, 31].

Furthermore, monocytes in HIV infection readily form cholesterol-laden foam cells [32, 33], and impaired HDL-mediated reverse cholesterol transport may be a contributing factor. HIV can directly block ATP-binding cassette transporter A1 (ABCA-1)-mediated cholesterol efflux to HDL particles, resulting in intracellular accumulation of lipids and enhanced foam cell formation [34, 35]. HIV RNA levels also correlate inversely with HDL concentrations [33]. Acute inflammatory responses, independent of HIV infection, may similarly alter HDL levels and impair cholesterol efflux from macrophages [25]. Low HDL levels have been observed in individuals with acute infections, systemic lupus erythematosus, and rheumatoid arthritis, and cholesterol efflux is impaired in animal models of sepsis [29, 36–38]. Modulation of lipid metabolism during chronic infection may be, in part, a non-specific consequence of inflammation.

Conventional lipid assessments performed routinely in clinics may not adequately assess perturbations in overall lipid profiles or sufficiently inform clinicians to CVD risk in HIV+ individuals [39]. Alterations in lipid particle composition and size tend to correlate more strongly with CVD risk than traditional lipid measurements in the HIV+ population [40, 41]. HDL and LDL particles are heterogeneous in size; large HDL is more cardioprotective [42], whereas small, dense LDL particles are associated with increased clinical and subclinical presentation of CVD [43, 44]. In a study examining ART-treated HIV+ individuals with benign traditional lipid panels, these individuals actually had pro-atherogenic lipid profiles with elevated small LDL particle numbers and reduced large HDL particles and impaired cholesterol efflux capacity [45]. Advanced lipid phenotyping by nuclear magnetic resonance spectroscopy may capture lipid-induced CVD progression better than traditional lipid measurements.

Few studies have investigated the complex relationships among the initiation of ART, lipid particle size and function, and CVD outcomes in HIV infection. In the AIDS Clinical Trials Group (ACTG) A5248 trial [46, 47•, 48, 49], treatment naïve HIV+ individuals initiating a "lipid friendly" raltegravir-based ART regimen were followed longitudinally; and after 48 weeks of ART, LDL levels were increased, but HDL composition and efflux capacity were improved [47•]. These findings would not have been evident when monitoring traditional lipid panels alone. Measurements of cholesterol particle size, composition, and function will likely improve the identification of HIV+ individuals with elevated CVD risk. Lo and colleagues also reported improvement in cholesterol efflux capacity following ART initiation, and this improvement was independently associated with a reduction in HIV viremia [50]. Further studies, comparing the effects various ART regimens on lipid particles and cholesterol efflux, should be considered.

Dyslipidemia and Chronic Immune Activation in HIV Infection

Chronic immune activation is a characteristic of ART-treated HIV infection and is likely driven by multiple factors [51]. Persistent inflammation underlies the development of many diseases, including atherosclerosis [52], and the inflammatory environment in HIV infection may accelerate progression of CVD. Further, there is a complex relationship between inflammation and the lipidome, as inflammatory processes can alter lipid metabolism, but many lipid species may also exacerbate persistent inflammation [5]. Thus, immune activation may be both a cause and a consequence of lipid abnormalities in HIV infection. Similarly, other chronic inflammatory diseases, including rheumatoid arthritis, systemic lupus erythematosus, and psoriasis, have also been linked to atherogenic lipid profiles [53].

Increased plasma levels of IL-6, C-reactive protein (CRP), and the coagulation marker D-dimer independently predict cardiovascular events and overall mortality in ART-treated HIV+ individuals [40, 54, 55]. Importantly, these markers were more strongly predictive of mortality in HIV+ individuals than in HIV− individuals [56–58], indicating that persistent inflammation plays a more critical role in morbidity and mortality in the context of HIV infection than it does for the general population. The Strategies for Management of Antiretroviral Therapy (SMART) study also demonstrated that lower total, large, and small HDL concentrations were associated with a higher risk for CVD in HIV+ individuals [40]. Moreover, this work identified an inverse relationship between HDL particle numbers and IL-6 and D-dimer levels. In patients initiating ART, HDL concentration increased; yet, the degree to which HDL levels were improved was dependent on levels of inflammation present at baseline [59]. In a separate study of ART-treated HIV+ individuals, metabolic factors, such as LDL and ApoA1, a major protein component of HDL, correlated even more strongly with CVD risk than did inflammatory biomarkers (CRP, IL-6, TNF-α) [60]. There is likely a complex relationship among HIV-associated dyslipidemia, activation of inflammatory pathways, and CVD risk.

Detailed Lipidomic Analyses Have Identified Lipid Profiles Associated with CVD

In contrast to basic lipid panels routinely performed in the clinic, detailed lipidomic analysis employs techniques to characterize lipid content in its entirety. Advances in multiple approaches for quantitative mass spectrometry (MS)-based lipid analyses (liquid chromatography, shotgun lipidomics, ion-mobility [61]) allow for more sensitive and extensive assessments of the complete lipidome [62–64] and have enabled the identification of over 40 different lipid classes and thousands of individual lipid species. Lipidomics has broad applications, including providing an important tool for identifying lipid biomarkers relevant to human disease.

Novel lipid biomarkers are predictive of NAFLD, systemic lupus erythematous, preeclampsia, and certain cancers [65–70]. Importantly, lipidomic profiling has also outperformed traditional lipid panels for prediction of CVD risk [39, 71, 72]. The prospective population-based Bruneck study identified 135 plasma lipid species from eight different lipid classes (phosphatidylcholine (PC), lysophosphatidylcholine (LPC), cholesterol ester (CE), sphingomyelin (SM), phosphatidylserine (PS), phosphatidylethanolamine (PE), lysophosphatidylethanolamine (LPE), triacylglycerol/triglycerides (TAG)) that were associated significantly with CVD events [73]. Moreover, there was significant overlap among plasma lipids associated with CVD and lipids previously determined to be enriched in plaques [74], suggesting that circulating lipids reflect disease progression in the atherosclerotic plaque. Of particular importance, the CVD-associated lipids, TAG(54:2), CE(16:1), and PE(36:5), outperformed traditional lipid panels for CVD risk stratification, and in network analyses, were highly interconnected with other lipids predictive of CVD. Furthermore, substitution of standard lipid measurements of Framingham Risk Score (HDL, TC) with TAG(54:2), CE(16:1), and PE(36:5) significantly improved 10-year risk classification [73].

Elevated TAG levels have been linked previously to insulin resistance and increased diabetes risk [75] and were implicated as an independent risk factor for CVD [76]. TAG concentrations increase during HIV infection [28] and are related to poor control of virus and higher circulating TNF-α levels, which may interfere further with lipid metabolism [72, 77]. More recent lipidomic analyses, however, have implicated specific TAG species as being more predictive of CVD compared with total TAG levels [71, 73–75]. The fatty acid

composition of TAGs is also important, as TAGs containing myristic acid (14:0), palmitic acid (16:0), stearic acid (18:0), myristoleic acid (14:1), palmitoleic acid (16:1), and oleic acid (18:1) are more closely associated with CVD than other fatty acids [73]. Similar trends among the fatty acid composition of TAGs, CEs, SMs, and free fatty acids (FFA) were also linked to increased CVD risk in both the Bruneck study and TwinsUK cohort [78].

In a study of HIV− individuals with asymptomatic or symptomatic CVD, 150 lipid species were uniquely enriched in atherosclerotic plaques, and further, distinct lipid signatures distinguished stable and unstable plaques [74]. Additionally, in a cohort of patients with coronary artery disease (CAD), lipidomic analyses more accurately characterized stable and unstable CAD than did traditional lipid measurements, with specific ceramides (CER) having even more predictive potential than LDL levels [79]. CERs have diverse pro-inflammatory properties. In mouse models, CERs induce NF-κB activation and inflammatory cytokine production [80], and CER levels are associated with chronic heart failure and all-cause mortality in humans [79, 81–83].

Integration of lipidomic data with other –omics strategies will likely enhance understanding of the mechanisms underlying the pathogenesis of CVD and allow for dynamic metabolic pathway reconstruction. An analysis of the Malmo Diet and Cancer (MDC) study cohort demonstrated significant relationships among plasma levels of specific lipid species that correlated with CVD events and validated CVD-associated gene variants [71]. Several of these gene variants were also directly involved in coding for lipid biosynthesis enzymes. Bridging lipidomics with genomics data may identify important links between lipids and genetic susceptibility for CVD.

The Altered Lipidome in HIV Infection

Recent lipidomic analyses have begun to elucidate lipidome abnormalities characteristic of HIV infection. Wong et al. reported altered levels of 7 lipid classes and 83 individual lipid species that were associated with HIV infection [72]. Further analyses identified associations among diacylglycerols (DAGs), phosphatidylinositol (PI), phosphatidylglycerol (PG), TAGs, CERs, PEs, LPEs, and CEs with CVD risk in HIV+ individuals. Individual DAG and TAG lipid biomarkers were most strongly associated with elevated risk for future CVD events and outperformed clinical measurements for risk assessment. Similar risk-associated profiles have been related to CVD and diabetes risk in HIV− populations [11, 84, 85]. Currently, no studies have explored changes in the lipidome pre- and directly post-HIV infection. HIV itself can modulate levels of fatty acid synthase [86], an enzyme important in de novo fatty acid synthesis, and as a consequence, may alter cell associated and plasma lipid profiles. One could speculate that the changes in the lipidome induced by HIV replication during acute or chronic infection may differ from the lipidome within that individual following viral suppression by ART.

Few studies have investigated dynamic changes to lipidome composition following initiation of ART. In a substudy of the ACTG A5248 trial [46–49], plasma concentrations and fatty acid composition of over 1300 different lipid species across 14 lipid classes were profiled in longitudinal samples from treatment naïve HIV+ individuals initiating a raltegravir-based ART regimen and following 48 weeks of ART [87•]. There were broad alterations in lipidome composition after 48 weeks of ART compared with HIV+ individuals at baseline and when compared with levels in cross-sectional samples obtained from age and sex matched HIV− individuals. Multiple individual lipid species previously linked to CVD-risk in the HIV− population were also increased in HIV+ individuals [88]. Notably, the concentration of LPC was increased significantly in HIV+ individuals at baseline and remained elevated after ART treatment. Increased LPC levels have also been observed in CVD and diabetes [14, 89, 90]. Furthermore, the fatty acid composition of LPC particles plays an important role in function. LPCs containing saturated fatty acids (SaFAs) are pro-inflammatory, whereas polyunsaturated fatty acid (PUFA)-containing LPCs are anti-inflammatory [14]. The A5248 study also demonstrated that levels of SaFAs, including palmitic acid (16:0) and stearic acid (18:0), were enriched among samples from the HIV population at baseline and after ART administration, and these SaFAs were directly related to levels of immune activation (sCD14, sTNF-R1, IL-6). Elevated circulating SaFAs are associated with greater risk of CVD in HIV− populations [91] and may similarly promote chronic inflammation and the development of comorbidities in HIV+ individuals [87•, 92].

In vitro exposure of myeloid cells to SaFAs induces inflammasome activation, TLR signaling, and secretion of inflammatory cytokines (IL-6, TNF-α, and IL-1β) [92–95]. In contrast, PUFAs inhibit inflammation [14, 96–98] and may protect against the development of diabetes, obesity, NAFLD, and NASH [10–13]. Moreover, depletion of PUFAs has been associated with hepatic triglyceride accumulation and endoplasmic reticulum stress [99, 100]. By interacting with PPAR transcription factors, PUFAs modulate fatty acid oxidation pathways and the inflammatory mediators, NF-kB, AP-1, NFAT, and STATs [101]. Furthermore, LDL particles composed of PUFA-containing cholesterol esters are thought to be less atherogenic; LDL particles enriched with SaFAs tend to be larger and more readily bind arterial proteoglycans, leading to atherosclerotic lesion formation [102]. In the A5248 trial, PUFA levels were reduced in HIV+ individuals at baseline, but improved following 48 weeks of ART [87•]. Imbalanced proportions of SaFAs and PUFAs may contribute to chronic inflammation and directly alter progression of diseases, including CVD and HIV infection. The precise

mechanisms by which lipidome perturbations mediate CVD development need to be explored.

As part of the Alternative Antiretroviral strategies: a comparison of three Initial Regimens (ALTAIR) trial, plasma lipidomic analyses were performed on a subset of treatment-naïve HIV+ individuals randomized to one of three initial ART regimens (efavirenz-, ritonavir-boosted atazanavir-, or zidovudine/abacavir-based regimens) [103•]. Following 48 weeks of ART, numerous lipid alterations were observed, and changes in lipid levels differed by treatment group. In the efavirenz cohort, concentrations of PI, PC, and sphingolipids were increased compared with baseline, whereas monohexoslyceramide and G_{M3} ganglioside classes were decreased with atazanavir/r, and there were no significant changes in lipid class concentrations with zidovudine/abacavir [103•]. Overall, consistently elevated lipid concentrations were measured in individuals taking efavirenz compared with the atazanavir/r and zidovudine/abacavir populations. Previous studies have suggested that efavirenz-induced dyslipidemia does not alter LDL/HDL ratio and is therefore not particularly atherogenic [104]; however, analyses of the US veterans affairs database have recently identified a potential link between efavirenz treatment and increased cardiovascular events [105]. Distinct efavirenz-induced lipidome alterations, particularly increased sphingolipid levels, which are predictive of symptomatic CAD [79], may better explain clinical outcomes in HIV+ individuals on this ART regimen.

The mechanisms by which various ART drugs affect lipid metabolism and contribute to dyslipidemia are different [4]; therefore, it is reasonable to assume that characteristic lipidome alterations in HIV+ individuals will differ depending on specific ART regimen. Further in-depth studies are warranted to characterize unique ART-associated lipid profiles in treated HIV infection and the clinical relevance of these lipid alterations. There is also a significant gap in knowledge regarding the dynamics of age-related effects on lipidome composition, and comprehensive longitudinal aging studies should be performed to identify lipid perturbations associated with age. Previously, increased incidence of insulin resistance and triglyceride accumulation was observed in elderly study populations [106, 107]. Lipid abnormalities may play a particularly important role in comorbidity risk in the aging HIV population. Future lipidomic analyses should also explore the contributions of lifestyle factors, such as diet and smoking status, infection with copathogens, and the composition of the microbiome on lipid profiles in HIV infection.

Strategies to Improve Lipids in HIV+ Individuals

The potential link between dyslipidemia and increased risk for CVD in chronic HIV infection has led to strategies for modulating lipid levels and mitigating inflammation in HIV+ individuals. Multiple studies have examined the efficacy of statin (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) usage in improving lipid profiles in HIV+ individuals and have reported beneficial effects on inflammatory markers and CVD risk with statin use [108–111]. In the Stopping Atherosclerosis and Treating Unhealthy Bone with Rosuvastatin in HIV (SATURN-HIV) trial, ART-treated HIV+ individuals with normal LDL levels, but increased biomarkers of immune activation, had reductions in T cell and monocyte activation markers, reduced vascular inflammation, and improved renal function following statin treatment [110–112]. Plasma levels of sCD14, a biomarker linked to morbidity and mortality in HIV infection [113], were also decreased by statin treatment. In a separate study, atorvastatin treatment resulted in reduced non-calcified plaque volumes in HIV+ individuals [114]. Additionally, statin use has been associated with decreased levels of oxidized LDL (OxLDL), a principal component in atherosclerotic lesions that is associated with plaque instability [109, 110, 114–116]. Changes in OxLDL levels were directly related to decreases in sCD14, tissue factor expression on monocytes, and improved carotid intima-media thickness (cIMT) measurements [115].

In a recent analysis, current lipid guidelines in place for the general population would not have recommended statins to the majority (~ 74%) of HIV+ individuals that did, in fact, have subclinical high-risk plaques [117]. Additional factors may need to be considered when identifying subgroups of the HIV+ population that could benefit from statin use. The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) study is currently evaluating the efficacy of statin use in preventing CVD events in HIV+ individuals that would be considered low risk based on current guidelines [118, 119]. Future studies should also take into account varying effects of different statins on specific lipid profiles. Comparative lipidomic analyses have demonstrated unique lipid species alterations induced differentially by rosuvastatin and atorvastatin, despite similar overall LDL lowering effects [120].

Lifestyle intervention studies, including changes in diet and exercise, may also prove useful in favorably modulating lipid levels and improving CVD outcomes in the HIV+ population. The American Heart Association (AHA) has long recommended reducing dietary saturated fat intake to protect against CVD [121]. In randomized, controlled trials, reductions in SaFA consumption and subsequent increases in PUFA intake reduced the incidence of CVD in the general population [91, 122]. Furthermore, several clinical studies have reported promising beneficial effects of PUFA supplementation on hypertriglyceridemia, hypertension, inflammation, and insulin sensitivity [123–126]; however, there is some disagreement concerning the association of fatty acid intake and clinical outcomes [91, 127]. In a randomized placebo-controlled trial,

oral supplementation of the PUFAs, EPA (20:5) and DHA (22:6), reduced inflammation and soluble TNFR1 levels in HIV+ individuals [128]. Studies that examine relationships among dietary and lifestyle interventions, the lipidome, inflammation, and comorbidities in HIV+ individuals should be pursued.

Conclusions

Chronic HIV infection and its treatment are associated with altered lipid profiles and increased risk for CVD. These lipid abnormalities are complicated further by persistent inflammation in treated HIV+ individuals that may also accelerate progression of CVD. Characterizing alterations in the lipidome of HIV+ individuals will likely help to identify metabolic abnormalities and elucidate determinants of enhanced CVD risk. Developing strategies to improve clinical management of CVD in the HIV+ population will be important, as guidelines in place for the general population may not adequately address the needs of HIV+ individuals. Further lipidomic analyses may provide novel drug targets and lipid biomarkers with greater diagnostic and prognostic value than traditional lipid analyses and supplement understanding of risk for comorbidity in HIV infection.

Compliance with Ethical Standards

Conflict of Interest Dr. Bowman declares that she has no conflict of interest.

Dr. Funderburg serves as a consultant for Gilead.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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