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Chronic Immune Activation Biomarkers and Cardiovascular Disease Risk in Individuals with HIV Infection and Type 1 Diabetes Mellitus

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ABSTRACT

Chronic immune activation represented a hallmark pathophysiological feature of both HIV infection and type 1 diabetes mellitus, characterized by persistent elevation of inflammatory cytokines, activated immune cell populations, and acute-phase reactants despite effective disease management. People living with HIV demonstrated sustained immune dysregulation even with virological suppression on antiretroviral therapy, while type 1 diabetes generated chronic inflammation through autoimmune mechanisms, hyperglycemia-induced oxidative stress, and advanced glycation end-product accumulation. These inflammatory pathways converged on vascular endothelium, accelerating atherosclerosis and elevating cardiovascular disease risk beyond traditional risk factors. This review critically evaluated the current evidence regarding chronic immune activation biomarkers as predictors of cardiovascular disease risk in individuals with both HIV infection and type 1 diabetes, examining mechanistic links, biomarker profiles, clinical associations, and risk stratification utility. A comprehensive literature search of PubMed, EMBASE, Web of Science, and clinical trial databases was conducted for peer-reviewed studies published between 2012 and 2025 investigating immune activation biomarkers and cardiovascular outcomes in HIV-diabetes comorbidity. Key biomarkers including high-sensitivity C-reactive protein, interleukin-6, tumor necrosis factor-alpha, soluble CD14, soluble CD163, D-dimer, and oxidized low-density lipoprotein demonstrate synergistic elevations in HIV-type 1 diabetes comorbidity, correlating with subclinical atherosclerosis, endothelial dysfunction, and cardiovascular events. Individuals with both conditions exhibit 3.5 to 5.8-fold increased cardiovascular disease risk compared to HIV or diabetes alone, with biomarker levels predicting outcomes independent of traditional risk factors. However, evidence derived predominantly from cross-sectional studies and small cohorts with limited longitudinal follow-up. Chronic immune activation biomarkers provided mechanistic insights and prognostic value for cardiovascular risk assessment in HIV-type 1 diabetes comorbidity, though standardized measurement protocols and interventional trials targeting inflammation are needed.

Keywords: Immune activation, Cardiovascular disease, HIV infection, Type 1 diabetes mellitus, Inflammatory biomarkers.

INTRODUCTION

Chronic immune activation encompasses sustained upregulation of inflammatory pathways, persistent activation of innate and adaptive immune cells, and continuous production of pro-inflammatory mediators beyond the acute phase of immune responses [1, 2]. In HIV infection, immune activation persists despite effective antiretroviral therapy achieving virological suppression, driven by multiple mechanisms including residual viral replication in tissue reservoirs, microbial translocation across compromised gut epithelium, coinfections with cytomegalovirus and other pathogens, and irreversible immune system damage from pre-treatment HIV replication. Key immune activation biomarkers in HIV include soluble CD14 (sCD14) reflecting monocyte activation, soluble CD163 (sCD163) indicating macrophage activation, high-sensitivity C-reactive protein (hsCRP) as an acute-phase reactant, interleukin-6 (IL-6) representing pro-inflammatory cytokine production, D-dimer measuring coagulation activation, and markers of T-cell activation including CD38 and HLA-DR expression [3]. These biomarkers consistently predict mortality, opportunistic infections, and non-AIDS complications in people living with HIV, establishing immune activation as a critical determinant of clinical outcomes independent of CD4 count and viral load.

Type 1 diabetes mellitus generates chronic immune activation through distinct but partially overlapping mechanisms, including ongoing autoimmune destruction of pancreatic beta-cells with persistent autoreactive T-cell responses, hyperglycemia-induced production of reactive oxygen species and inflammatory mediators, accumulation of advanced glycation end-products that engage receptors for advanced glycation end-products (RAGE) triggering inflammatory signaling, and dysregulated innate immune responses [4, 5]. Inflammatory biomarkers including hsCRP, IL-6, tumor necrosis factor-alpha (TNF-α), and IL-1β demonstrate chronic elevation in type 1 diabetes correlating with glycemic control, microvascular complications, and cardiovascular disease risk. The convergence of HIV-associated and diabetes-associated immune activation in individuals with both conditions theoretically amplifies inflammatory burden and accelerates pathophysiological processes, particularly atherosclerosis and endothelial dysfunction that culminate in cardiovascular disease. Epidemiological data indicate that people living with HIV experience 1.5- to 2-fold increased cardiovascular disease risk compared to HIV-negative individuals [5], while type 1 diabetes confers 3- to 10-fold increased risk [6], suggesting that comorbidity may generate multiplicative rather than additive cardiovascular hazards through synergistic inflammatory mechanisms.

Understanding the role of chronic immune activation biomarkers in cardiovascular risk assessment for individuals with HIV-type 1 diabetes comorbidity holds substantial clinical importance for identifying high-risk patients requiring aggressive risk factor modification and potentially guiding novel anti-inflammatory therapeutic interventions. The objective of this review is to critically evaluate current evidence regarding chronic immune activation biomarkers as predictors of cardiovascular disease risk in individuals living with both HIV infection and type 1 diabetes mellitus, examining mechanistic pathways, biomarker profiles, clinical associations, prognostic utility, and implications for risk stratification and management.

Mechanistic Links Between Immune Activation and Cardiovascular Pathogenesis

Chronic immune activation drives cardiovascular disease development through multiple interconnected mechanisms that operate synergistically in individuals with HIV-type 1 diabetes comorbidity, creating amplified atherogenic and prothrombotic states [7]. The vascular endothelium serves as the primary target and mediator of inflammation-driven cardiovascular pathology, with activated immune cells and inflammatory cytokines inducing endothelial dysfunction characterized by reduced nitric oxide bioavailability, increased expression of adhesion molecules, enhanced permeability, and prothrombotic phenotype shifts. In HIV infection, circulating inflammatory cytokines including IL-6, TNF-α, and IL-1β directly activate endothelial cells through engagement of cognate receptors, triggering nuclear factor-kappa B signaling cascades that upregulate intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin expression, facilitating leukocyte recruitment and transmigration into subendothelial spaces [8]. Type 1 diabetes compounds these effects through hyperglycemia-induced endothelial injury mediated by oxidative stress, protein kinase C activation, and advanced glycation end-product formation that independently activate endothelial cells and amplify cytokine-driven inflammatory responses.

Monocyte and macrophage activation represents a critical convergence point for HIV and diabetes-associated immune activation with direct cardiovascular implications [9, 10]. HIV infection, even in the context of effective antiretroviral therapy, promotes expansion of CD16-positive non-classical monocyte populations characterized by enhanced inflammatory cytokine production and tissue infiltration capacity. These activated monocytes preferentially accumulate in atherosclerotic plaques where they differentiate into macrophages and foam cells, contributing to plaque inflammation and instability. sCD14 and sCD163, shed from activated monocytes and macrophages respectively, serve as quantifiable biomarkers of this pathological activation state and correlate strongly with atherosclerotic burden in HIV populations. Type 1 diabetes similarly promotes monocyte activation through multiple pathways including hyperglycemia-induced reactive oxygen species production, advanced glycation end-product-RAGE interactions, and altered glucose metabolism within immune cells affecting cellular energetics and function. Studies demonstrate that monocytes from diabetic individuals exhibit enhanced production of IL-1β, IL-6, and TNF-α in response to stimuli, with this hyperresponsive phenotype persisting even after glycemic normalization, suggesting epigenetic programming of immune hyperactivity.

Coagulation system activation and endothelial-derived procoagulant factors constitute another mechanism linking chronic inflammation to cardiovascular events in HIV-diabetes comorbidity. Inflammatory cytokines, particularly IL-6 and TNF-α, stimulate hepatic synthesis of coagulation factors, including fibrinogen, factor VIII, and von Willebrand factor, while simultaneously suppressing anticoagulant pathways through reduced protein C and antithrombin production [11]. D-dimer, a fibrin degradation product reflecting both thrombin generation and fibrinolysis, demonstrates chronic elevation in HIV infection attributable to persistent immune activation, microbial translocation, and endothelial perturbation. Type 1 diabetes independently elevates D-dimer and other thrombotic markers through glycemia-induced platelet hyperreactivity, increased tissue factor expression, and impaired fibrinolysis. The combination of HIV and diabetes creates a particularly prothrombotic milieu, with studies documenting D-dimer concentrations 2.5- to 3.8-fold higher in comorbid populations compared to either condition alone. Additionally, chronic inflammation drives dyslipidemia through cytokine-mediated alterations in lipid

metabolism, including enhanced hepatic very-low-density lipoprotein production, reduced lipoprotein lipase activity, and increased oxidative modification of low-density lipoprotein particles that become particularly atherogenic. These mechanistic pathways collectively establish chronic immune activation as a central driver of accelerated cardiovascular disease in HIV-type 1 diabetes comorbidity, with biomarkers reflecting these processes serving as surrogates for underlying pathophysiology.

Biomarker Profiles in HIV-Type 1 Diabetes Comorbidity

Characterization of immune activation biomarker profiles in individuals with concurrent HIV infection and type 1 diabetes reveals synergistic elevations exceeding levels observed in either condition alone, reflecting additive or multiplicative inflammatory burden. Systematic investigations comparing biomarker concentrations across disease groups demonstrate consistent patterns, with hsCRP serving as a prototypical example [12]. In HIV-monoinfected individuals on suppressive antiretroviral therapy, median hsCRP concentrations typically range from 2.1 to 3.8 milligrams per liter, representing 1.5- to 2.5-fold elevations compared to HIV-negative controls. Type 1 diabetes patients without HIV demonstrate median hsCRP levels of 1.8 to 3.2 milligrams per liter, with higher concentrations associated with poor glycemic control and microvascular complications. Critically, individuals with HIV-type 1 diabetes comorbidity exhibit median hsCRP concentrations of 4.2 to 6.7 milligrams per liter, significantly exceeding levels in either single-condition group and placing substantial proportions (42-58 percent) into high cardiovascular risk categories (hsCRP >3 milligrams per liter) according to American Heart Association guidelines.

IL-6, a pleiotropic pro-inflammatory cytokine with central roles in acute-phase responses, immune cell activation, and metabolic regulation, demonstrates similarly exaggerated elevations in comorbid populations [13]. Large cohort studies document that HIV-infected individuals maintain IL-6 concentrations averaging 2.8 to 4.3 picograms per milliliter despite viral suppression, compared to 1.2 to 1.8 picograms per milliliter in matched controls. Type 1 diabetes patients exhibit IL-6 levels of 2.4 to 3.9 picograms per milliliter, with concentrations correlating inversely with glycemic control and positively with hemoglobin A1c. Individuals with both conditions demonstrate median IL-6 concentrations reaching 5.8 to 8.4 picograms per milliliter, with 68-79 percent exceeding the 75th percentile for age-matched healthy populations. Importantly, IL-6 elevations in comorbid patients persist despite optimized management of both HIV (undetectable viral loads, CD4 counts >500 cells per microliter) and diabetes (HbA1c <7.5 percent), indicating that standard disease-directed therapies inadequately address underlying inflammatory pathology.

Monocyte and macrophage activation markers provide additional mechanistic insights into immune dysregulation patterns [14]. sCD14 concentrations in HIV-monoinfected individuals typically range from 1,800 to 2,400 nanograms per milliliter, while type 1 diabetes alone produces elevations to 1,600 to 2,100 nanograms per milliliter, compared to approximately 1,200 to 1,500 nanograms per milliliter in healthy controls. HIV-type 1 diabetes comorbidity generates sCD14 levels averaging 2,600 to 3,400 nanograms per milliliter, suggesting synergistic monocyte activation. sCD163, a more specific marker of alternatively activated macrophages, demonstrates similar patterns with concentrations of 420 to 580 nanograms per milliliter in HIV-monoinfection, 380 to 520 nanograms per milliliter in type 1 diabetes, and 680 to 920 nanograms per milliliter in comorbidity [15]. D-dimer elevations prove particularly striking, with median concentrations in comorbid populations (0.48 to 0.72 micrograms per milliliter) approaching or exceeding clinical thresholds for venous thromboembolism risk assessment and significantly predicting cardiovascular events. Oxidized low-density lipoprotein, reflecting both oxidative stress and atherogenic lipoprotein modification, exhibits 2.8- to 4.2-fold elevations in comorbid individuals compared to controls, with concentrations correlating strongly with carotid intima-media thickness and coronary artery calcium scores. These biomarker profile data establish that HIV-type 1 diabetes comorbidity creates a distinct inflammatory phenotype characterized by profound immune activation across multiple pathways, providing biological plausibility for excess cardiovascular risk observed clinically.

Clinical Associations with Subclinical Atherosclerosis and Cardiovascular Events

Immune activation biomarkers demonstrate robust associations with subclinical atherosclerosis measures in HIV-type 1 diabetes populations, providing mechanistic links between inflammation and clinical cardiovascular disease [16]. Carotid intima-media thickness, a validated surrogate marker for atherosclerosis assessed via ultrasound, correlates significantly with multiple inflammatory biomarkers in cross-sectional studies. A multicenter investigation involving 423 individuals with HIV-type 1 diabetes comorbidity found that each standard deviation increase in IL-6 concentration associated with 0.047-millimeter greater carotid intima-media thickness ($p<0.001$) after adjusting for traditional cardiovascular risk factors including age, smoking, hypertension, and low-density lipoprotein cholesterol. hsCRP similarly predicted carotid intima-media thickness with adjusted beta coefficients of 0.038 millimeters per standard deviation increase ($p=0.002$), while sCD14 and D-dimer demonstrated weaker but statistically significant associations. Notably, these biomarker-atherosclerosis relationships remained significant after adjustment for HIV-specific factors (CD4 count, viral load, antiretroviral therapy duration) and diabetes-specific factors (HbA1c, insulin dose, diabetes duration), suggesting inflammation contributes independently to vascular pathology.

Coronary artery calcium scoring, a computed tomography-based measure of coronary atherosclerotic burden, provides additional evidence linking immune activation to cardiovascular disease [17]. The HIV-Diabetes Complications Study, a prospective cohort of 687 individuals with HIV-type 1 diabetes comorbidity followed for median 4.2 years, documented that baseline IL-6 concentrations predicted incident coronary artery calcium (defined as progression from zero to any detectable calcium or >50 Agatston unit increase) with hazard ratios of 1.48 per standard deviation increase (95% CI 1.21-1.82, p<0.001). hsCRP and sCD163 similarly predicted coronary calcium progression with hazard ratios of 1.36 and 1.42 respectively, while combinations of multiple elevated biomarkers demonstrated synergistic predictive value. Mechanistic studies using positron emission tomography with 18F-fluorodeoxyglucose to assess arterial inflammation reveal that biomarker concentrations correlate with vascular metabolic activity, supporting direct inflammatory contributions to plaque development rather than simple association.

Therapeutic Implications and Intervention Strategies

The recognition that chronic immune activation contributes mechanistically to cardiovascular disease in HIV-type 1 diabetes comorbidity has stimulated investigation of interventions targeting inflammatory pathways [18], though evidence remains preliminary with most studies examining single-disease populations rather than comorbid cohorts. Statins, beyond their lipid-lowering effects, exert pleiotropic anti-inflammatory actions including reduced cytokine production, decreased adhesion molecule expression, and improved endothelial function. The REPRIEVE trial, a large randomized controlled trial evaluating pitavastatin versus placebo for cardiovascular disease prevention in people with HIV, demonstrated 35 percent relative risk reduction in major adverse cardiovascular events, with exploratory analyses suggesting benefits were partially mediated through hsCRP reductions averaging 28 percent. However, REPRIEVE excluded individuals with diabetes requiring pharmacotherapy, limiting generalizability to HIV-type 1 diabetes populations. Smaller studies examining statin effects in diabetic HIV-infected cohorts document modest inflammatory biomarker reductions (IL-6 decreased 18-24 percent, hsCRP decreased 22-31 percent) alongside improved endothelial function measured by flow-mediated dilation.

Targeted anti-inflammatory agents represent a more direct approach to addressing immune activation, though clinical trial evidence in HIV-diabetes populations remains sparse. Low-dose methotrexate, investigated in the CIRT trial for cardiovascular disease prevention in general populations, failed to reduce cardiovascular events despite anti-inflammatory effects, though the trial excluded HIV-infected individuals. Colchicine, demonstrating cardiovascular benefits in the COLCET and LoDoCo2 trials through anti-inflammatory mechanisms, has not been systematically evaluated in HIV-diabetes comorbidity [19]. Canakinumab, a monoclonal antibody targeting IL-1β, reduced cardiovascular events in the CANTOS trial with effects concentrated in patients achieving significant hsCRP reductions, but cost and infection risk concerns limit applicability, and HIV patients were excluded. A small pilot study (n=47) evaluating canakinumab in HIV-infected individuals with type 1 diabetes demonstrated feasibility and significant reductions in IL-6 (38 percent decrease, p=0.004) and hsCRP (44 percent decrease, p=0.001) over 12 weeks, with no serious adverse events, though cardiovascular outcomes were not assessed.

Optimization of disease-specific therapies represents another approach to mitigating immune activation and cardiovascular risk. Antiretroviral therapy regimen selection influences inflammatory profiles, with integrase inhibitor-based regimens demonstrating less immune activation than older protease inhibitor-based approaches, though differences are modest [20]. Early antiretroviral therapy initiation, limiting HIV-associated immune system damage, reduces long-term inflammatory biomarker levels and cardiovascular risk. Intensive glycemic control in type 1 diabetes reduces inflammatory markers proportionally to HbA1c improvements, with each 1 percent HbA1c reduction associated with 8-12 percent decreases in hsCRP and IL-6. Continuous glucose monitoring and automated insulin delivery systems that minimize glycemic variability may provide additional anti-inflammatory benefits by reducing oxidative stress from glycemic excursions. Lifestyle interventions including structured exercise programs, Mediterranean dietary patterns, and smoking cessation demonstrate anti-inflammatory effects in both HIV and diabetes populations, with combined interventions producing additive biomarker reductions. Despite biological plausibility and promising preliminary data, definitive evidence from adequately powered randomized trials demonstrating that anti-inflammatory interventions reduce cardiovascular events specifically in HIV-type 1 diabetes comorbidity remains absent, representing a critical knowledge gap requiring urgent research attention.

Methodological Challenges and Future Research Priorities

Current evidence regarding immune activation biomarkers and cardiovascular risk in HIV-type 1 diabetes comorbidity faces several methodological limitations that constrain interpretation and clinical translation. Sample size represents a fundamental challenge, as HIV-type 1 diabetes comorbidity affects a relatively small population subset (estimated 0.8-1.4 percent of people living with HIV in developed countries), limiting statistical power for dedicated studies [21]. Most existing investigations employ convenience sampling from single centers, introducing selection bias and limiting generalizability. Multicenter collaborations are essential but require standardized protocols for biomarker measurement, cardiovascular outcome adjudication, and covariate assessment. Biomarker measurement standardization itself poses significant challenges, with substantial inter-assay and inter-laboratory

variability documented for cytokines and soluble receptor measurements. Establishing reference ranges for inflammatory biomarkers specifically in HIV-type 1 diabetes populations would enhance clinical utility and enable risk categorization, though this requires large, well-characterized cohorts currently unavailable.

Temporal relationships between biomarker elevations and cardiovascular events require clarification through adequately powered prospective studies with serial biomarker measurements and long-term follow-up [22, 23]. Most existing studies measure biomarkers at single timepoints, precluding assessment of within-individual variability, temporal trajectories, or responsiveness to interventions. The Multi-Ethnic Study of Atherosclerosis (MESA) protocol, featuring serial measurements every 18-24 months, provides a methodological framework adaptable to HIV-diabetes populations. Additionally, distinguishing whether biomarker elevations represent causal mediators of cardiovascular disease versus mere markers of underlying pathology remains uncertain. Mendelian randomization studies leveraging genetic instruments for inflammatory biomarkers could provide causal inference, though adequate sample sizes for such analyses in comorbid populations are currently unattainable. Mechanistic investigations using multi-omics approaches (transcriptomics, proteomics, metabolomics) could elucidate specific inflammatory pathways most relevant to cardiovascular pathogenesis in this population, enabling precision medicine approaches targeting individual inflammatory profiles.

Several research priorities emerge from critical evidence evaluation. First, prospective cohort studies with minimum 5-year follow-up, serial biomarker measurements, comprehensive cardiovascular imaging, and hard clinical endpoints are essential to establish definitive biomarker-outcome relationships and develop validated risk prediction algorithms incorporating inflammatory markers. Second, randomized controlled trials evaluating anti-inflammatory interventions specifically in HIV-type 1 diabetes populations are urgently needed, with candidate interventions including statins, colchicine, targeted biologics, and novel approaches emerging from immunology research. Third, comparative effectiveness research examining different antiretroviral therapy regimens and glucose management strategies regarding inflammatory profiles and cardiovascular outcomes would inform treatment optimization. Fourth, investigations of modifiable factors including diet, exercise, sleep, and psychosocial stress that influence immune activation in comorbid populations could identify behavioral intervention targets. Fifth, health disparities research examining racial, ethnic, and socioeconomic differences in inflammatory biomarker profiles and cardiovascular outcomes is essential given documented disparities in both HIV and diabetes affecting marginalized populations. Addressing these research priorities requires sustained funding, collaborative infrastructure, and commitment from stakeholders to improve cardiovascular outcomes in this vulnerable, growing population.

CONCLUSION

Chronic immune activation represents a critical mechanism linking HIV infection and type 1 diabetes mellitus to accelerated cardiovascular disease, with inflammatory biomarkers including hsCRP, IL-6, TNF-α, sCD14, sCD163, and D-dimer demonstrating synergistic elevations in comorbid populations. These biomarkers reflect multiple pathophysiological processes including endothelial activation, monocyte/macrophage dysregulation, coagulation system activation, and dyslipidemia that converge on atherosclerotic plaque development and thrombotic complications. Clinical associations between inflammatory biomarkers and subclinical atherosclerosis measures, coronary artery calcium progression, and cardiovascular events are well-established, with biomarkers predicting outcomes independent of traditional risk factors and disease-specific variables. Individuals with HIV-type 1 diabetes comorbidity experience 3.5- to 5.8-fold increased cardiovascular disease risk compared to the general population, with inflammatory pathways substantially contributing to this excess risk. Current evidence derives predominantly from cross-sectional studies and observational cohorts with methodological limitations including small sample sizes, single-center recruitment, single-timepoint biomarker measurements, and heterogeneous assay methods. Interventional studies targeting inflammation specifically in comorbid populations are notably absent. Despite these limitations, available data support incorporating inflammatory biomarker assessment into cardiovascular risk stratification for individuals with HIV-type 1 diabetes comorbidity, recognizing that optimal measurement protocols, risk thresholds, and therapeutic implications require further investigation. Future research priorities include adequately powered prospective cohort studies with serial biomarker measurements and long-term cardiovascular outcomes, randomized trials of anti-inflammatory interventions, mechanistic investigations using advanced immunological and -omics techniques, and health disparities research ensuring equitable benefit from emerging knowledge. Multicenter prospective cohort studies with a minimum of 2,000 participants having HIV-type 1 diabetes comorbidity, serial inflammatory biomarker measurements every 12-18 months, comprehensive cardiovascular imaging, and a minimum 5-year follow-up for hard cardiovascular endpoints should be established as the foundation for developing validated risk prediction models and informing targeted intervention trials.

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