With improving long-term survival after successful suppression of HIV replication, cardiovascular disease (CVD) is an increasingly important health problem facing HIV infected (HIV+) people. Antiretroviral therapy itself, conventional Framingham risk factors, anemia, hepatitis C co-infection, and renal disease are all risk factors among HIV+ people, but these factors do not completely explain the excess risk of CVD among HIV+ compared to uninfected (HIV-) people. Based on insights gained largely from murine models, progressive atherosclerosis largely causes CVD which is in turn caused by inappropriate lipid metabolism and activation of the innate and adaptive immune systems. While alteration in immune cell function is a shared feature of HIV and CVD pathogenesis, it is not known whether the activation, number and or proportion of peripheral circulating monocyte and T cell subsets are associated with incident CVD in humans and explain the excess risk of CVD among HIV+ people compared to HIV- people. To answer these questions, we will leverage the Veterans Aging Cohort Study (VACS) biomarker cohort, a longitudinal, prospective observational cohort of 1525 HIV+ and 853 HIV- Veterans. Important strengths of this cohort include existing stored cryopreserved cells, data on biomarkers of inflammation, coagulation, and monocyte activation; longitudinal survey, Medicare, Medicaid, mortality and national death index data; comprehensive access to the entire VA electronic medical record including pharmacy records; and adjudicated CVD events occurring within and outside the VA. We propose to measure immune cell types and subsets from existing cryopreserved cells collected in 2005-2006 and (2) to adjudicate CVD events (i.e., acute myocardial infarction, coronary heart disease, ischemic stroke, heart failure, and CVD death) from 2005-2017. Our specific aims are to: (1) Determine the number and proportion of pro and anti-atherosclerotic immune cells as well as naïve and memory/effector T cells among HIV+ and HIV- people; (2) Determine if these immune cell types and subsets are independently associated with prevalent and incident CVD; (3) Determine whether they mediate the association between HIV infection and incident CVD. We hypothesize that people with (1) a higher proportion of proatherosclerotic (e.g., intermediate monocytes and T_{H1} cells) and a lower proportion of anti-atherosclerotic (e.g., T_{H} regulatory cells) immune cells, respectively, and/or (3) increased evidence of immunosenescence (e.g., a low ratio of naive: memory T cells) will have an increased risk of incident CVD and that these types of immune cell subsets will explain the excess risk of CVD among HIV+ people compared to HIV- people. If our hypotheses are true, we will advance our understanding of how immune function contributes to CVD for HIV+ and HIV- people while also potentially identifying new targets for future CVD intervention studies and new risk factors for inclusion into current CVD risk prediction tools. In addition, the VACS biomarker cohort will become a valuable resource for the larger research community interested in immune function and CVD and other lung and blood disorders.