The Role of Monocytes in Promoting Atherosclerosis in Virologically Suppressed People Living with HIV (PLWH)

Anthony Jaworowski[1,2], Anna C. Hearps[2,3], T.A. Angelovich[1], Janine Trevillyan[2] and Jennifer F. Hoy[2].

1. *School of Health and Biomedical Sciences, RMIT University, Melbourne, 3083*
2. *Dept of Infectious Diseases, Alfred Hospital and Monash University, Melbourne, 3004*
3. *Life Sciences Discipline, Burnet Institute, Melbourne, 3004*

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in PLWH, the most common cause of which is coronary artery disease caused by atherosclerotic plaque formation in peripheral and coronary arteries. Risk of CVD in PLWH is increased by multiple factors including traditional risk factors, cumulative use of antiretroviral drugs and persistent inflammation.

Antiretroviral therapy does not efficiently decrease myeloid cell activation as shown by persistence of soluble plasma markers of monocyte/macrophage activation and of surface activation markers on monocytes. There is recent evidence using FDG-positron emission tomography for accumulation of activated monocyte-derived macrophages in the ascending aortic arch of PLWH, consistent with myeloid and endothelial activation. Importantly, this accumulation is not decreased following lipid lowering therapy, consistent with mechanisms independent of dyslipidemia. Our laboratory has also shown that monocytes from virologically-suppressed PLWH have an atherogenic phenotype consisting of increased pro-inflammatory responses to pathogen ligands, decreased cholesterol efflux capacity and impaired reverse endothelial transmigration. Taken together these properties predict an increased tendency of monocytes from these individuals to migrate into sites of activated endothelia on arteries and mature into lipid-laden foam cells which initiate atherosclerotic plaque formation. Using an in vitro model of transendothelial migration and foam cell formation we have shown that monocytes from virologically-suppressed PLWH demonstrate these properties *ex vi*vo. Our recent data from PLWH and HIV-negative control subjects matched for age, sex, smoking and BMI show that the monocyte atherogenic phenotype declines very slowly after initiation of antiretroviral therapy and more than a decade of effective viral suppression is required to return these monocyte properties to control levels.

PLWH should be monitored for CVD risk and managed appropriately. Measures of monocyte activation may be useful in predicting risk not accounted for by traditional risk factors or dyslipidemia.