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Dr. Currier has been involved in the conduct of clinical research studies focused on improving the treatment of HIV infection. Her work has been conducted through the NIAID funded AIDS Clinical Trials and through industry funded studies. Dr. Currier is the Principal Investigator for the UCLA AIDS Prevention and Treatment Clinical Trials Unit and Vice Chair of the AIDS Clinical Trials Group (ACTG). Her areas of research focus include understanding the pathogenesis and management of long term complications of HIV disease, specifically cardiovascular and metabolic complications associated with HIV treatment. In addition she has led several studies focused on women with HIV from the perspective of HIV treatment and long term outcomes.

"It is very difficult to sort out the contributions of HIV and HAART as it pertains to risk of CVD, but I would say that HIV is the stronger factor.
Several studies have suggested that the relative risk of CVD in HIV patients is higher for women than it is for men, however the absolute rates are higher in men than in women".

A case-control comparison of men with and without HIV found that higher arterial inflammation in the HIV-positive men was significantly associated with bone marrow and splenic metabolic activity. Principal investigator Priscilla Hsue (University of California, San Francisco, UCSF) believes her findings suggest that the spleen--often regarded as a superfluous organ--may play a critical role in the heightened inflammation and cardiovascular risk seen in people with HIV. Hsue noted that chronic monocyte/macrophage activation probably explains the increased arterial inflammation and cardiovascular risk in people with HIV. Arterial inflammation measured by FDG-PET/CT scans correlates with monocyte/mac-

rophage activity and predicts cardiovascular disease. The monocyte/macrophages of interest, Hsue said, come from bone marrow and transiently reside in spleen. After myocardial infarction, monocyte/macrophages migrate from the spleen to injured tissue, where they participate in regulation of inflammation and development of heart failure. Research also shows that the spleen is a major reservoir for HIV during antiretroviral therapy. To explore the relationship between spleen and bone marrow metabolic activity and FDG-PET/CT-measured vascular inflammation, Hsue and colleagues conducted a case-control study. Cases were 27 HIV-positive men in the UCSF SCOPE cohort. The investigators matched each HIV-positive man to an HIV-negative man by age and Framingham risk score. The HIV group included 16 antiretroviral-treated men with viral suppression, 7 elite controllers (who suppress HIV RNA without treatment), and 4 untreated noncontrollers. In the HIV-positive and negative groups, median age stood at 54 and 55 and median Framingham risk score at 6% and 5%. A lower proportion of men with HIV were white (52% versus 89%), a marginally higher proportion had diabetes (7% versus 0%), a slightly lower proportion had hypertension (30% versus 37%), and a higher proportion currently smoked (37% versus 19%). Lipid levels were similar in cases and controls, except for lower median triglycerides in the HIV group (89 versus 119 mg/dL). Median duration of HIV infection stood at 21.5 years in treated controllers, 23 years in elite controllers, and 3 years in untreated noncontrollers. Current median CD4 counts in the three groups were 591, 1075, and 664. The treated group had taken antiretrovirals for a median 9.1 years. All treated men and all elite controllers had a viral load below 75 copies. Four treated men and 2 elite controllers had HCV infection, while none of the 4 untreated men did. FDG-PET/CT-measured metabolic activity was significantly greater in HIV-positive than negative men in aorta (2.8 versus 2.2 standardized uptake values [SUV], $P < 0.0001$), bone marrow (3.6 versus 2.5 SUV, $P = 0.0002$), and spleen (3.3 versus 2.4 SUV, $P = 0.0001$). When Hsue and colleagues limited the analysis to the 16 antiretroviral-treated men, results were nearly identical and significant for each comparison. Vascular inflammation correlated strongly with splenic metabolic activity in HIV-positive men (Spearman correlation 0.53, $P = 0.014$) and even more strongly in HIV-negative men (Spearman correlation 0.73, $P = 0.00016$). Vascular inflammation also correlated with splenic metabolic activity in the antiretroviral-treated subgroup, but that correlation fell short of statistical significance (Spearman correlation 0.46, $P = 0.13$). Bone marrow metabolic activity correlated strongly with vascular inflammation in men with HIV (Spearman correlation 0.80, $P < 0.0001$) and HIV-negative men (Spearman correlation 0.78, $P = 0.00014$). The correlation remained significant when the researchers limited the analysis to antiretroviral-treated men (Spearman correlation 0.84, $P = 0.0026$). Bone marrow metabolic activity also correlated with splenic activity in men with HIV (Spearman correlation 0.51, $P = 0.052$) and HIV-negative men (Spearman correlation 0.59, $P = 0.020$). Vascular, bone marrow metabolic activity, and splenic activity did not correlate with metabolic activity in two control tissues--pectoralis muscle and subcutaneous fat. In the antiretroviral-treated group, five markers of inflammation were significantly associated with vascular inflammation and eight were not. Integrated HIV DNA was not associated with vascular inflammation in these men. Four inflammation markers were associated with splenic metabolic activity in antiretroviral-treated men, as was integrated HIV DNA (RR 1.14, 95% CI 1.04 to 1.26, $P = 0.008$). The 0.47 Spearman correlation between integrated HIV DNA and splenic metabolic activity stopped short of statistical significance ($P = 0.17$). Hsue cautioned that her study is small and "hypothesis generating." She also noted that, despite matching, cases differed somewhat from controls in ways that could affect metabolic activity and inflammation. But with those caveats in mind, she concluded that these HIV-positive men had significantly higher levels of vascular inflammation, splenic tissue metabolic activity, and bone marrow activity than men without HIV. The correlations between splenic and bone marrow activity and vascular inflammation, she proposed, suggest a systemic inflammatory disease. The investigators proposed that "the spleen and bone marrow may represent a key reservoir for HIV" and that "HIV may cause activation of inflammatory cells in the spleen resulting

in elevated cardiovascular risk."

A study of 41 people on stable antiretroviral therapy (ART) with no history of heart disease linked PET scan-measured arterial inflammation to high-risk coronary artery plaques. The finding extends the understanding of heightened cardiovascular disease risk in people with HIV. Several studies confirm higher cardiovascular disease rates in men and women with HIV than in the general population. Although reasonable explanations for this association abound, research has not nailed down a physiologic mechanism. To address this question, Markella Zanni and Massachusetts General Hospital (MGH) colleagues explored potential links between arterial inflammation and high-risk coronary artery plaques in HIV-positive people with subclinical coronary atherosclerosis. Using coronary computed tomography angiography (CTA), the MGH group previously found a higher prevalence of high-risk coronary plaques (those with a tendency to rupture) in HIV-positive than HIV-negative people. Work by the MGH team and others used PET scans to determine that HIV-positive people have higher rates of arterial inflammation than people without HIV. In the new study Zanni and colleagues set out to see whether these two pieces of evidence fit together. They focused on 41 HIV-positive people on stable antiretroviral therapy and without a cardiovascular disease history but with subclinical atherosclerosis indicated by coronary plaque on CTA. The researchers divided this group into 21 people with arterial inflammation below the group median and 20 with inflammation above the group median (PET-determined target-to-background ratio [TBR] of 2.17). The high-inflammation group had a higher proportion of men than the low-inflammation group (95% versus 67%, P = 0.02) and a lower average CD4 count (485 versus 699, P = 0.04). But the groups did not differ in age (average 51 overall), current smoking (30%), diabetes (10%), 10-year Framingham risk score (6), HIV duration (15 years), antiretroviral duration (11 years), nadir CD4 count (199), or viral load (47 copies/mL). People in the high-inflammation group did not differ from those in the low-inflammation group in average number of plaques per person (3.6 in both groups). But the high-inflammation group had a higher average number of high-risk plaque features in the highest-risk plaques (1.3 versus 0.8, P = 0.02) and a higher number of low-attenuation plaques (average 0.5 versus 0.1 per person, P = 0.02). Among people in the high-inflammation group, 40% had at least one low-attention plaque, compared with 10% of the low-inflammation group (P = 0.02). The high- and low-inflammation groups also differed in the proportion with at least one plaque that had two high-risk features (35% versus 10%, P = 0.04). Multivariate modeling determined that both median TBR in the high-inflammation group (beta estimate 0.35, P = 0.004) and HIV duration (beta estimate 0.04, P = 0.05) were associated with number of low-attenuation plaques per person. Gender, CD4 count, and LDL cholesterol were not associated with number of low-attenuation plaques in this analysis. The MGH team concluded that their findings "are the first to demonstrate a relationship between arterial inflammation and high-risk morphology coronary plaque in HIV-positive patients." They cautioned that their analysis is limited by measurement of arterial inflammation in the aorta rather than coronary arteries, the small sample size, and the cross-sectional design. The researchers called for further study to determine whether arterial inflammation measured over time predisposes HIV-positive people to high-risk plaques and to test inflammation-quelling strategies to see if they prevent plaque rupture and myocardial infarction.

HIV infection--independently of classic risk factors--nearly tripled the risk of cardiovascular disease in a study of more than 2000 women in the US Veterans Aging Cohort Study. Higher heart disease risk with versus without HIV held true regardless of CD4 count. But women with a viral load below 500 copies did not have a higher cardiovascular disease risk than women without HIV, whereas women with a viral load above 500 copies did. Several studies have found higher rates of cardiovascular disease in women with HIV than in the general population. But these studies often could not assess the impact of key risk factors such as smoking and HCV infection. To determine whether HIV by itself confers a higher risk of cardiovascular disease in women, Julie Womack (Yale University) and colleagues at

other institutions analyzed cardiovascular disease incidence in women enrolled in the Veterans Aging Cohort Study Virtual Cohort, who have free access to HIV care. All women were free of cardiovascular disease at their first clinical visit on April 1, 2003 or later. Observation continued until a first cardiovascular diagnosis (acute myocardial infarction, heart failure, or ischemic stroke), death, or December 31, 2009. Cox proportional hazards models to assess the impact of HIV on incident cardiovascular disease adjusted for age, race/ethnicity, lipids, smoking, blood pressure, diabetes, renal disease, obesity, hepatitis C, and substance use. The study included 2190 women, 710 of them (32%) with HIV infection. In the groups with and without HIV, age (mean 43.2 and 44.0), race (61.6% and 59.4% African American), and Framingham cardiovascular risk score (mean 3.2 and 3.1) did not differ much. A higher proportion of women with HIV currently smoked (59.2% versus 40.5%), had HCV infection (24.4% versus 5.7%), abused alcohol (13.8% versus 5.0%), and abused cocaine (13.5% versus 3.6%). Almost half of HIV-negative women (44.6%) were obese, compared with one quarter of HIV-positive women (25.3%). Among women with HIV, CD4 count averaged 468 and viral load 57,866 copies. Most women, 58.7%, were not taking antiretrovirals. Through a median follow-up of 6 years, 86 women had a cardiovascular diagnosis, 46 of them (53%) with HIV infection. Cardiovascular disease-free survival over this time was significantly diminished in women with HIV compared with HIV-negative women ($P < 0.001$). A Cox model adjusted for both demographic and Framingham cardiovascular risk factors determined that HIV infection independently tripled the risk of cardiovascular disease (adjusted hazard ratio [aHR] 2.8, 95% confidence interval [CI] 1.7 to 4.6). Other independent risk factors were hypertension (aHR 2.4, 95% CI 1.5 to 3.8), cocaine abuse or dependence (aHR 2.5, 95% CI 1.1 to 5.4), and older age. Factors not associated with cardiovascular risk in this analysis were race (black versus white), diabetes, lipids, smoking, statin use, hepatitis C, alcohol use or dependence, and body mass index. Womack and colleagues then explored associations between HIV and cardiovascular disease according to CD4 count, viral load, and antiretroviral use. Compared with HIV-negative women, HIV-positive women in every CD4 stratum analyzed had an independently higher risk of cardiovascular disease:
-- 500 or more CD4s: aHR 2.3, 95% CI 1.3 to 4.4
-- 200 to 499 CD4s: aHR 2.9, 95% CI 1.5 to 5.7
-- Under 200 CD4s: aHR 3.8, 95% CI 1.9 to 7.6
Cardiovascular risk did not differ between women in these three CD4 strata. Compared with HIV-negative women, positive women with a viral load at or above 500 copies had almost a quadrupled risk of cardiovascular disease (aHR 3.7, 95% CI 2.2 to 6.5). But HIV-positive women with a viral load below 500 copies did not have a higher cardiovascular disease risk than HIV-negative women, and risk did not differ between the two HIV groups. Antiretroviral-treated women with a viral load at or above 500 copies had more than a quadrupled cardiovascular disease risk than women without HIV (aHR 4.4, 95% CI 2.0 to 10.0). But antiretroviral-treated women with a sub-500 viral load did not have a higher cardiovascular disease risk than HIV-negative women. HIV-positive women not taking antiretrovirals had a tripled risk of cardiovascular disease compared with HIV-negative women (aHR 3.0, 95% CI 1.8 to 5.1). Again, these three HIV groups did not differ from each other in cardiovascular disease risk. The investigators believe their findings "have important policy and clinical implications given the growing number of HIV-positive women and the fact that heart disease is the leading cause of death among women in the US." They call for further research to explore etiology and predictors of heart disease in HIV-positive women.