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Cardiovascular Disease in Adult and Pediatric HIV/AIDS

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It may surprise some to learn that the National Heart, Lung, and Blood Institute (NHLBI) has been funding research on the cardiovascular complications of HIV/AIDS for well over twenty years. We present a brief overview and an update on NHLBI-funded cardiovascular research in HIV/AIDS.

Since it was first recognized clinically in 1981, HIV/AIDS has gone from a fatal syndrome to a chronic disease in individuals receiving highly active antiretroviral therapy (HAART). Though the first antiretroviral agent, zidovudine (AZT), was introduced into the market in 1987, the era of HAART really began after the marketing approval of the first protease inhibitor in December of 1995. Much has been reported about the relationship between HAART and cardiovascular disease (CVD), but it is this combination antiretroviral therapy that has allowed the overall mortality of HIV to decline dramatically and life expectancy to increase to the point where CVD-related deaths now represent an increasing proportion of the deaths in HIV-infected patients.

Even prior to the era of HAART researchers noted that untreated HIV-infected patients had altered lipid profiles, including lowered high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol levels, elevated triglyceride levels, and anthropomorphic changes such as increased visceral fat and decreased subcutaneous fat (1,2). With the widespread use of HAART, the contribution of drug-related metabolic and anthropometric alterations to an increased risk for CVD took on an even greater significance. Several studies in adult populations have provided evidence of an association between HIV infection and its treatment and CVD, including retrospective studies such as the Kaiser Permanente Registry study (3), prospective observational cohort studies such as the Data Collection of Adverse Events of Anti-HIV Drugs (DAD) study (4,5), and prospective randomized clinical trials such as the Strategies for Management of Antiretroviral Therapy (SMART) trial (6). Though myriad class-specific and non-class specific effects on lipid profiles, glucose levels and insulin sensitivity, and body composition have been reported with various antiretroviral agents, there

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is no question that the use of HAART to ensure adequate viral suppression is paramount to the successful clinical management of HIV-infected patients.

The currently available evidence from various studies suggests that though the overall cardiovascular event rate is low, there is an excess risk of cardiovascular events in HIV-infected persons compared to non-HIV infected individuals. Evidence suggests that HIV-infected individuals on HAART regimens are at increased risk of dyslipidemia, ischemic heart disease (7), and myocardial infarction, particularly if the HAART regimen contains a protease inhibitor (8,9). While lipid lowering therapies are a routine element of cardiovascular risk reduction in the general population, HIV-infected persons may not be receiving lipid lowering therapies even when indicated. A recent report showed that among those meeting the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) criteria (10), there was a disparity in receipt of lipid lowering agents among HIV-infected veterans compared to HIV-uninfected veterans (15.4% vs. 37.9% $p < 0.01$) (11). In 2003 the Infectious Diseases Society of America (IDSA) and the Adult AIDS Clinical Trials Group (AACTG) issued an updated version of "Guidelines for the Evaluation and Management of Dyslipidemia in Human Immunodeficiency Virus-Infected Adults Receiving Antiretroviral Therapy" (http://www.idsociety.org/content.aspx?id=9202#md) (12). HIV-infected patients may have special issues, such as co-infection with hepatitis C, seemingly complicated medication regimens, unusually high triglyceride levels, or the need to gain weight yet achieve lower lipid levels; but, the approach to the management of their dyslipidemia is essentially the same as that for the general population, including starting with non-drug and dietary modalities. If lipid-lowering agents are indicated, navigating the sea of potential drug-drug interactions with the HAART regimen can be challenging, but this should not preclude the use of drugs such as statins or fibrates in HIV-infected patients. Getting to target LDL goals can and should be accomplished by the Cardiologist working closely with the Infectious Diseases specialist (13).

Antiretroviral drugs are the cornerstone of HIV/AIDS management and they may be associated with insulin resistance and dyslipidemia, but they are not the only factors likely involved in the increased CVD risk seen in HIV-infected patients. Traditional risk factors may be increased in these patients, such as increased rates of smoking; HIV itself may affect traditional risk factors, including lipid profiles; and/or there may be increased underlying inflammation or endothelial dysfunction. How HIV affects the heart and vasculature as a whole in the presence of anti-retroviral therapy (ART) is not fully known, but left ventricular dysfunction is clinically common and pulmonary arterial hypertension can occur in 1 out of every 200 HIV+ adults, most often in patients without advanced HIV disease. In contrast to primary pulmonary hypertension (PPH) where there is a female predominance, males are more affected by pulmonary arterial hypertension associated with HIV infection (HIV-PAH). HIV-PAH shares several clinical and pathological features with PPH, but has decreased 1-year survival rates (51%) compared to rates in a National Institutes of Health registry for PPH (68%) (14). HIV-PAH patients have worse survival than HIV-infected patients without PAH and often die from conditions related to the pulmonary hypertension, not from the HIV infection *per se*. Therefore, prompt diagnosis and initiation of specific therapy such as a prostacyclin (epoprostenol) or the dual endothelin receptor antagonist bosentan is crucial (15). Isolated diastolic dysfunction may be an early sign of cardiovascular disease in both the general population and HIV-infected patients. A recent albeit small study reported an unexpectedly high prevalence of diastolic dysfunction (37%) in a cohort of young (median age=38 years), asymptomatic HIV-infected patients at otherwise low risk for cardiovascular disease (16). Consequently, although there are currently no recommendations for routine screening echocardiograms in this population, these data suggest such additional evaluations may be warranted in particular patients.

Research conducted prior to the HAART era demonstrated that HIV infection itself can cause nonatherosclerotic structural and functional injury to the heart and vasculature. In one of the first reports of cardiac disease in HIV-infected children, Lipshultz and colleagues reported abnormalities of left ventricular shortening, afterload, and contractility. Pericardial effusion, arrhythmias, and pathologic evidence of pericarditis, myocarditis, and inflammation of the conduction system were also observed (17). To address the high rates of cardiac complications seen in the HIV/AIDS epidemic, the NHLBI initiated the Pediatric Pulmonary and Cardiac Complications of Vertically Transmitted HIV Infection (P2C2 HIV) study in 1990 (18). The P2C2 HIV study was a prospective, observational study that enrolled HIV-infected children from 1990 to 1993 with follow-up to 10 years of age. The study documented cardiac complications as a common feature of HIV disease in children. The five-year cumulative incidence of depressed shortening fraction was 28%, the incidence of left ventricular end-diastolic dilation was 22%, and the incidence of heart failure and/or use of cardiac medications was 29% (19). Decreased left ventricular shortening and increased left ventricular wall thickness were found to be predictive of mortality even after adjusting for CD4 count and encephalopathy (20).

One of the great successes of HAART is the significant decrease in vertical transmission of HIV from mother to child, but this has led to an increasing cohort of antiretroviral therapy-exposed, HIV-negative children. Recent evidence suggests an important role of ART exposure itself in contributing to cardiac disease. The P2C2 HIV study documented diminished left ventricular shortening and contractility at birth in HIV-negative infants born to HIV-positive mothers suggesting that the *in utero* environment plays an important role in postnatal cardiovascular function. Animal model data have subsequently indicated that nucleoside analog reverse transcriptase inhibitors have a toxic effect on mitochondrial function (21). Further, human studies have demonstrated a depletion of mitochondrial DNA and elevated plasma lactate levels in HIV-negative infants born to zidovudine-treated, HIV-positive mothers (22). Taken together these data suggest potential cardiotoxic effects of ART-exposure *in utero*. Recently, more direct evidence for this association was provided by the CHAART-I study, in which serial echocardiograms from HIV-negative infants born to ART- or HAART-treated, HIV-positive mothers were compared to HIV-negative infants born to HIV-positive mothers who did not receive perinatal ART or HAART. A preliminary report from that study indicated that fetal exposure to ART/HAART was associated with progressive reductions in LV mass and septal wall thickness (23).

The NHLBI provides co-funding for the Eunice Kennedy Shriver National Institute of Child Health and Human Development-sponsored Pediatric HIV/AIDS Cohort Study (PHACS) network (http://www.nichd.nih.gov/research/supported/phacs.cfm). This network, established in 2005, seeks to advance our understanding of the long-term safety of fetal and infant exposure to prophylactic ART and the effects of perinatally acquired HIV infection in adolescents. The network currently supports two prospective, observational cohort studies (SMARTT and AMP), both with significant cardiovascular components.

The Surveillance Monitoring for ART Toxicities (SMARTT) Study (not to be confused with the SMART study in adults) follows the ART-exposed, but HIV-uninfected, infants and children born to HIV-infected mothers to evaluate for conditions and diagnoses potentially related to *in utero* and infantile exposure to antiretroviral therapies. The study will identify abnormalities in cardiac function related to ART and/or HIV exposure and examine the utility of serum biomarkers as surrogates of cardiac dysfunction.

The Adolescent Master Protocol (AMP) cohort consists of perinatally exposed, HIV-infected children between the ages of 7 and 16 years and a comparison group of perinatally exposed, HIV-uninfected children. The goal of the study is to evaluate the impact of HIV infection and

ART on pre-adolescents and adolescents with perinatal HIV infection. Cardiac function will be evaluated by echocardiography to estimate the prevalence of structural and functional abnormalities in this contemporary cohort of HIV-infected youths.

Recently published work has demonstrated that, similar to adults, the use of protease inhibitors in HIV-infected children is significantly correlated with elevated triglyceride and LDL-cholesterol levels and with reduced HDL-cholesterol levels (24). What this means in terms of cardiovascular risk for HIV-infected children, in the face of lifelong antiretroviral therapy, is unknown.

A State of the Science Conference was convened in Chicago in June 2007 to examine the important unanswered questions surrounding the pathogenesis, detection, and treatment of cardiovascular disease in HIV-infected individuals (25). Following this conference the NHLBI issued a Request for Applications (RFA) for research on the mechanisms and management of cardiovascular and metabolic complications of HIV/AIDS. The NHLBI awarded grants to eight primary research sites and a clinical coordinating center, representing a spectrum of HIV-infected patients and controls including men and women, children, individuals with long-standing infection, and newly diagnosed and/or treatment-naïve patients. Some of the areas under investigation in this program include: the role of oxidative stress and inflammation in elevated CV risk; the effect of antiretroviral therapies on endothelial function and atherosclerosis progression; immune, inflammatory, coagulation, and lipid alterations as mediators of increased atherosclerosis; and assessments of vascular dysfunction due to HIV itself and metabolic parameters. The various studies include standard and novel imaging techniques as well as measurements of endothelial function. The awardees have worked together closely to develop a core set of, and standardized approaches to, laboratory evaluations. The results from these studies are sure to add to our knowledge of cardiovascular disease and its management in HIV/AIDS, with the possibility for advancing our understanding of cardiovascular disease in general.

The NHLBI encourages the continued partnership of basic and clinical cardiovascular and infectious diseases researchers in their effort to tackle the difficult and still unanswered questions of cardiovascular disease in HIV/AIDS.

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