

## Effects of HIV Infection and Antiretroviral Therapy on the Heart and Vasculature

Michael P. Dubé, MD, Co-Chair; Steven E. Lipshultz, MD, Co-Chair; Carl J. Fichtenbaum, MD; Richard Greenberg, MD; Alison D. Schechter, MD; Stacy D. Fisher, MD; for Working Group 3

Both infection with human immunodeficiency virus (HIV) and treatment of HIV infection with antiretroviral drugs may affect the function of the heart and the vasculature. Direct infection of target tissues with HIV, inflammation and immunosuppression secondary to HIV infection, and common comorbidities, such as alcohol and drug abuse, may all contribute to impairment of function. Direct effects of antiretroviral drugs on the vasculature and indirect effects mediated through the metabolic complications of antiretroviral therapy (ART)<sup>1</sup> also appear to contribute to this impairment. The landmark Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study found that use of HIV-1 protease inhibitors is associated with an increased risk of myocardial infarction,<sup>2</sup> but only part of this increased risk is mediated by the circulating lipid disturbances these drugs induce. Thus, other mechanisms by which protease inhibitors cause endothelial dysfunction, insulin resistance, and enhanced atherosclerosis are likely to be involved.

### Effects of HIV Infection

#### Effect of HIV Infection on the Developed Heart

HIV infects myocytes but is not abundant (1 in  $\geq 2000$  cells) or highly multiplicative in these cells.<sup>3</sup> Despite the paucity of evidence of direct myocyte involvement, HIV infection clearly causes structural and functional injury to the heart as a whole. The virus persists in reservoir cells in the cerebral cortex and in macrophages that may be present between myocardial cells, even after effective ART.<sup>4</sup> Much of the evidence for HIV effects on the heart was published before the era of highly active ART (HAART), and thus, the

beneficial effects on the heart of more thorough suppression of HIV infection with HAART are generally less well understood.

Reservoir cells and associated cytokine signaling may be important in the development and progression of cardiomyopathy and encephalopathy. Reservoir cells may hold HIV on their surfaces for extended periods. It is also possible that the reservoir is in cytoplasmic vacuoles, with virus inducible through the Golgi apparatus, where progressive tissue damage is caused by virus-induced chronic release of cytotoxic cytokines.<sup>4</sup>

Left ventricular (LV) dysfunction causes symptomatic heart failure and occurs at unexpected rates in HIV-infected individuals. Cardiovascular abnormalities are common in HIV-infected individuals but often go unrecognized or untreated, which results in increased cardiovascular-related morbidity and mortality and reduced quality of life. Clinicians may mistakenly attribute signs of cardiovascular abnormalities to pulmonary or infectious causes, an error that can delay appropriate treatment.<sup>5</sup>

Signs and symptoms of heart failure in these patients may be atypical or masked by concurrent illness, dehydration, or malnutrition. Electrocardiography may reveal nonspecific conduction defects or repolarization changes. Up to 57% of asymptomatic HIV-infected patients have ECG abnormalities, including supraventricular and ventricular ectopic beats and nonspecific ST-T-wave abnormalities.<sup>6</sup> Cardiomegaly or pulmonary congestion may be evident on chest radiographs. Elevated brain natriuretic peptide levels may be helpful for the diagnosis of cardiomyopathy.<sup>7</sup> Echocardiography, the

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only specific test for LV systolic dysfunction in this population, often reveals increased LV mass with low-normal or increased wall thickness and a dilated LV. Because symptoms are often nonspecific and may be difficult to distinguish from pulmonary infection, echocardiographic measurements are diagnostic.

Cardiomyopathy was accompanied by biopsy evidence of myocarditis in 63 of 76 adult patients in one study<sup>8</sup> and in half of the patients in another.<sup>9</sup> Patients with isolated right ventricular dysfunction or borderline LV dysfunction did not necessarily have a lower CD4 count and did not have an altered prognosis.<sup>8</sup> Cardiomyopathy associated with HIV infection carries a worse prognosis than other types of nonischemic cardiomyopathy.<sup>10</sup>

Nutritional deficiencies have been related to dilated cardiomyopathy in specific patients with carnitine and selenium deficiencies. The deficiencies recovered with replacement.<sup>5</sup> Rapid-onset congestive heart failure has a poor prognosis among HIV-infected patients.<sup>10</sup> Heart failure with gradual onset may respond better to medical therapy in these patients.

### Effects of HIV Infection on the Developing Heart

Progressive LV dilation in HIV-infected children without adequate compensatory hypertrophy results in excessive LV afterload, reduced LV function, and symptomatic cardiovascular disease. Children with inadequate compensation for LV hypertrophy treated in the pre-HAART era have a 5-year cumulative incidence of congestive heart failure of 12.3%.<sup>11</sup>

In a population of vertically infected children, inadequate or reduced LV wall thickness identified those at risk for death within 18 to 24 months and may thus be useful as an independent predictor of impending mortality.<sup>12</sup> Mildly increased LV mass is a marker for early HIV mortality. LV mass is elevated but is still inadequate for the dimensions of the ventricle.<sup>13</sup> A 2-standard deviation decrease in LV fractional shortening from 34% to 30% in a 10-year-old child, a decrease that most cardiologists would not consider to be "actionable," is associated with an increase in 5-year mortality from 15% to 55%.<sup>13</sup>

In another study, cardiac morbidity (including 10% with transient congestive heart failure, 10% with chronic congestive heart failure, and 9% with cardiac arrest) and mortality (including 33% deaths due to cardiac causes) were more common in more advanced disease, with coinfections, wasting, or encephalopathy.<sup>14</sup> Mortality was related to wasting, encephalopathy, low CD4 count, low immunoglobulin G (IgG) serum levels, earlier era, and male sex. Cardiac mortality was 35% in the Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection (P2C2) HIV longitudinal study of vertically infected children.<sup>15</sup> Routine echocardiographic screening of HIV-infected children is valuable because even minimally abnormal measurements are validated predictors of mortality, often identifying at-risk populations years before death.

Mean LV structure and function are more normal in HIV-infected children who receive monthly intravenous immunoglobulin therapy. Impaired myocardial growth and dysfunction may be immunologically mediated and responsive to immunomodulatory therapy.<sup>16</sup>

**Table. Mechanisms by Which HIV Infection and ART May Adversely Affect the Vasculature**

HIV infection
1. Endothelial dysfunction
2. Lipid disorders associated with HIV infection
3. Viral protein-related endothelial cell activation
4. Systemic inflammatory cytokine-chemokine dysregulation
5. Direct HIV infection of endothelium and vascular smooth muscle cells
6. Enhanced atheroma formation by activated macrophages
7. Prothrombotic state
ART
1. Endothelial dysfunction
2. Increased endothelial permeability
3. Increased oxidative stress
4. Increased mononuclear cell adhesion
5. Insulin resistance
6. Accelerated lipid accumulation in vessel wall
7. Persistent inflammation and immune activation
8. Impaired response to vascular injury
9. ART-associated lipodystrophy leading to metabolic disorders, increased systemic inflammation, and reduced circulating adiponectin

Troponin is a sensitive and specific marker of myocardial injury, and the performance of a troponin assay is helpful in a risk-benefit discussion about endomyocardial biopsy and in deciding the utility of intravenous immunoglobulin therapy in a particular patient. Right ventricular biopsy is likely underused in these patients.

### Effect of HIV Infection on the Vasculature

Endothelial dysfunction precedes and is related to the clinical manifestations of atherosclerosis.<sup>17</sup> Untreated HIV-infected patients have endothelial dysfunction that improves with ART<sup>18,19</sup> but that does not return to normal in the short term. Brachial flow-mediated dilation was impaired among ART-naïve subjects (median value of 3.7%, with values of 8% to 12% considered normal) but improved by a median of 1.5% with 24 weeks of ART.<sup>19</sup> This lack of more complete improvement may be the result of an insufficient observation period, a negative effect of antiretroviral drugs, or possibly persistent HIV-related inflammation and immune activation. Long-term studies of the course of this dysfunction are needed.

The mechanism of HIV-related endothelial dysfunction is not clear but may include lipid disorders associated with HIV infection,<sup>1</sup> viral protein-related endothelial activation,<sup>20</sup> effects of systemic inflammatory cytokine or chemokine dysregulation, or direct HIV infection of the endothelium<sup>21</sup> and vascular smooth muscle cells (Table). HIV-associated systemic inflammation may contribute to endothelial dysfunction, because treatment of HIV-infected individuals not receiving ART with the antiinflammatory agent salsalate improved endothelial dysfunction.<sup>22</sup> HIV-associated activated macrophages may predispose patients to endothelial dysfunction and enhance atheroma formation.<sup>23</sup> Activated

endothelial and vascular smooth muscle cells can contribute to a prothrombotic milieu.<sup>24</sup>

### Effect of HIV Infection on Pulmonary Circulation

Pulmonary arterial hypertension can occur in 1 of every 200 HIV-infected adults who are generally without advanced acquired immune deficiency syndrome (AIDS).<sup>25</sup> The pathophysiology is identical to that of idiopathic pulmonary arterial hypertension, with plexiform lesions and Heath-Edwards changes demonstrated histologically.<sup>26</sup> Clinical symptoms are nonspecific and may mimic right-sided heart failure or pulmonary infection.<sup>27</sup> Echocardiography is often diagnostic, revealing elevated pulmonary pressure estimates and possibly right ventricular hypertrophy, dysfunction, or both. The prognosis is poor, with a median survival of  $\approx$ 6 months, despite ART. Survival may improve with endothelin antagonists<sup>28</sup> and does improve with intravenous epoprostenol.<sup>29</sup>

### Other Nonatherosclerotic, HIV-Associated Cardiovascular Disorders

In HIV patients with nonatherosclerotic cardiac disease, prolonged QT intervals are common and may limit medical therapies.<sup>26</sup> Early clinical signs of autonomic dysfunction in HIV-infected individuals include syncope and presyncope, diminished sweating, diarrhea, bladder dysfunction, and impotence.<sup>26</sup> A careful history is key to taking proper precautions for procedures, such as cardiac monitoring and bedside atropine, because dysautonomia is common late in the disease state and may cause adverse anesthetic reactions.

Many types of vasculitis have been associated with HIV infection.<sup>26</sup> Pericardial effusions are generally small and asymptomatic, with an incidence as high as 11% per year in adults with AIDS.<sup>30</sup> In children with vertically transmitted HIV infection, pericardial effusions tend to occur less frequently, to be small, and to be nonprogressive.

Bacterial endocarditis in HIV-infected individuals is no more common than in cohorts with similar risk behaviors.<sup>26</sup> Nonbacterial thrombotic endocarditis involves large, friable, sterile vegetations that form on the cardiac valves, which are associated with disseminated intravascular coagulation and systemic embolization. Lesions are rarely diagnosed antemortem, but they cause clinically relevant emboli in an estimated 42% of patients with the diagnosis.<sup>8</sup> The risks and benefits of anticoagulation must be assessed on an individual basis.

## Effects of ART

### Effects of ART on the Developing and the Developed Heart

Compelling evidence from animal models indicates that thymidine analogs (zidovudine and stavudine) and didanosine have marked adverse effects on myocardial structure and function that are mediated by mitochondrial toxicity.<sup>31</sup> Abnormal myocardial mitochondrial function and depletion of mitochondrial DNA have been documented in these animal models.<sup>31</sup> Combination ART that includes an HIV-1 protease inhibitor, by altering myocardial glucose uptake via glut4 blockade,<sup>32</sup> may also predispose susceptible patients to myocardial dysfunction. However, clinical data linking specific

ART classes or agents with myocardial dysfunction in adult patients are lacking.

In children, strong evidence suggests that normal physiological myocardial hypertrophy is blunted. Exposure to ART in utero, even among children born without HIV infection, may ultimately have adverse clinical effects on cardiac structure and function.<sup>33</sup> During the first postnatal year, ART exposure during fetal and early postnatal life is associated with reductions in LV mass and septal wall thickness and with increased LV afterload.<sup>33</sup> However, ART exposure during fetal and early neonatal life is associated with more normal postnatal infant cardiac function and healthier mothers.

ART exposure during fetal and early neonatal life is also associated with impaired myocardial growth that is characterized by substantially lower LV wall thickness and mass, a situation reminiscent of anthracycline cardiotoxicity, in which late cardiac morbidity and mortality occur in long-term survivors. Continued use of ART to prevent mother-to-child transmission of HIV is critical because the proven benefit of preventing HIV infection with ART outweighs the theoretical risk of cardiac toxicity. Long-term follow-up of exposed children with and without HIV infection is critical, because they appear to be at risk for late cardiotoxicity.

### Effects of ART on the Vasculature

ART improves endothelial dysfunction in the short term, as measured by brachial flow-mediated dilation<sup>19</sup> and endothelial activation markers.<sup>18</sup> In contrast, 1 early study documented severe endothelial dysfunction in patients who received long-term, protease-inhibitor-based ART (mean duration of ART was 70 months, including 31 months of therapy with a protease inhibitor) but not in those receiving ART without a protease inhibitor.<sup>34</sup> Half of the patients received the older and now seldom-used protease inhibitor indinavir. More contemporary studies, in which few patients received indinavir, have not confirmed a role for protease-inhibitor-containing ART regimens in endothelial dysfunction.<sup>35</sup> Studies in HIV-uninfected patients show a marked effect of indinavir in inducing endothelial dysfunction<sup>36,37</sup> but suggest a beneficial<sup>38</sup> or neutral<sup>39</sup> effect with the protease inhibitor combination lopinavir-ritonavir, or with atazanavir,<sup>39</sup> on endothelial function.

These findings emphasize a major research limitation, which has been the tremendous heterogeneity in the metabolic effects of different protease inhibitors,<sup>1</sup> such that any particular adverse effect discovered with 1 drug should not generally be considered representative of the entire drug class. As a result, each protease inhibitor will have to be studied individually in a similar manner.

Experimental models suggest several possible mechanisms for protease-inhibitor-induced endothelial dysfunction. This dysfunction appears to be mediated by reduced nitric oxide production or release, on the basis of both clinical<sup>37</sup> and experimental<sup>40</sup> models. Specific mechanisms include reduced expression of endothelial nitric oxide synthase<sup>40</sup> and increased reactive oxygen species,<sup>41</sup> which may be ameliorated by certain antioxidants.<sup>41,42</sup> Clinical studies of the use of

antioxidants to ameliorate endothelial dysfunction in HIV-infected individuals have not been reported.

Experimental data suggest that protease inhibitors may promote atherosclerosis by effects other than those on circulating lipoprotein levels or endothelial dysfunction. These include impaired cholesterol efflux from foam cells<sup>43</sup> and increased macrophage cholesterol ester accumulation through upregulation of the CD36 scavenger receptor.<sup>44</sup> This latter effect may actually be favorably modulated by other concurrent antiretroviral medications, such as didanosine and stavudine.<sup>45</sup> Impaired endothelial regrowth due to ART after experimental arterial injury is another potential mechanism that predisposes to cardiovascular disease.<sup>46</sup>

The thymidine analog nucleoside reverse-transcriptase inhibitors stavudine and zidovudine may also directly and negatively affect endothelial function by increasing superoxide production, as shown in experimental models.<sup>47</sup> However, no clinical study data link any of the individual drugs in this class to endothelial dysfunction.

### Controversial Issues, Gaps in Knowledge, and Future Research Priorities

HIV-related cardiovascular disease is an underrecognized and underappreciated cause of symptomatic illness and a predictor of all-cause mortality in late-stage HIV infection. A high degree of suspicion and early screening may allow appropriate intervention and improved quality of life in those affected. Both HIV infection itself and various components of ART can impair the function of the heart and the vasculature. The potential mechanisms involved and their clinical relevance need further study.

Specific needs for future research include:

- Determining the mechanisms of myocardial dysfunction caused by HIV infection
- Assessing the prevalence and functional implications of HIV-related subclinical myocardial dysfunction
- Identifying biomarkers specific to HIV-infected patients to serve as surrogate end points for cardiovascular disease
- Establishing the role of host and viral factors (genetics and lifestyle choices) in the pathogenesis of cardiovascular disease
- Evaluating ART and other specific therapies for treating pulmonary arterial hypertension
- Comprehensively assessing the role of individual ART agents within each drug class in different experimental models
- Evaluating antioxidants and antiinflammatory agents in HIV and ART-related endothelial dysfunction
- Establishing a network of multidisciplinary, clinical research sites with the capability for detailed study of cardiovascular/metabolic complications of HIV disease and its treatment

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