

## Editorial

# The expanding role of the cardiologist in the care of HIV infected patients

Cardiovascular manifestations of HIV infection have been observed for more than 15 years and finally prospective data substantiates this association.<sup>1</sup> Studies published over the past 2–3 years have tracked the incidence and course of HIV infection in relation to cardiac illness in both children and adults (table 1). These recent studies show that subclinical echocardiographic abnormalities independently predict adverse outcomes and identify high risk groups to target for early intervention and treatment.

The introduction of highly active antiretroviral therapy (HAART) regimens has significantly modified the course of HIV disease, with longer survival rates and improvement of life quality in HIV infected subjects expected. However, early data raised concerns about HAART being associated with an increase in both peripheral and coronary arterial diseases.

Importantly, the studies listed in table 1 were performed in the era before HAART. Understanding the effects of HAART on the cardiovascular system is only possible by understanding the effects of HIV co-infections first. HAART is only available to a minority of HIV infected individuals worldwide and studies before HAART remain globally applicable. UNAIDS estimates that 36.1 million people were living with HIV infection at the end of the year 2000. If 8–10% of patients develop symptomatic heart failure over a 2–5 year period, then three million cases of HIV related heart failure will have presented in that time period.<sup>2</sup> Dilated cardiomyopathy, coronary artery disease, endocarditis, and pericardial effusion related to HIV infection will be reviewed here.

### Dilated cardiomyopathy

HIV disease is recognised as an important cause of dilated cardiomyopathy (fig 1), with a prevalence reported at 3.6% among cardiomyopathy patients, increasing as patients with HIV infection live longer.<sup>1</sup> Compared to patients with idiopathic dilated cardiomyopathy, those with HIV infection and dilated cardiomyopathy have greatly reduced survival and a hazard ratio of death of 4.0.<sup>3</sup> The importance of

cardiac dysfunction is demonstrated by a reported median survival to AIDS related death which is 101 days in patients with left ventricular dysfunction and 472 days in patients with a normal heart by echocardiography at similar infection stage.<sup>2</sup>

Myocarditis still represents the best studied cause of dilated cardiomyopathy in HIV disease.<sup>4</sup> HIV virions appear to infect myocardial cells in patchy distributions<sup>4</sup> without a clear direct association between HIV and cardiac myocyte dysfunction.<sup>4,5</sup> It is unclear how virus enters CD4 receptor negative cells such as myocytes. Reservoir cells (for example, dendritic cells) may play a pathogenic role in the interaction between HIV and the myocyte and in the activation of multifunctional cytokines that contribute to progressive and late tissue damage.<sup>3</sup> Asymptomatic left ventricular dysfunction and increased left ventricular mass independently predict accelerated mortality in both adults and children infected with HIV.<sup>6</sup> Treatment for dilated cardiomyopathy associated with HIV infection is generally similar to treatment for non-ischaemic cardiomyopathy. Angiotensin converting enzyme inhibitors are recommended based on general heart failure studies, but may be poorly tolerated because of low systemic vascular resistance from diarrhoeal disease, infection, or dehydration. No studies have investigated the efficacy of specific therapeutic regimens, including HAART, other than intravenous immunoglobulin.<sup>7</sup> The apparent efficacy of immunoglobulin treatment may be the result of immunoglobulins inhibiting cardiac autoantibodies by competing for Fc receptors or dampening the secretion or effects of cytokines and cellular growth factors.<sup>8</sup>

Encephalopathy influences negatively the clinical course of dilated cardiomyopathy in HIV disease. Several studies reported that patients with encephalopathy were more likely to die of congestive heart failure than were patients without encephalopathy with a hazard ratio after multivariate analysis of 3.4.<sup>9</sup> HIV may persist in reservoir cells in the myocardium and the cerebral cortex even after antiretroviral treatment.<sup>9</sup> The reservoir cells may hold HIV-1 on

Table 1 Selected long term prospective studies of HIV related cardiovascular disease

Author/study/date	n	Patients	Follow up (years)	Major findings
<i>Children</i>				
Lipshultz/ P <sup>2</sup> C <sup>2</sup> /2000 <sup>6</sup>	193	Vertical transmission median age 2.1 years	5	Lower left ventricular fractional shortening ( $p \leq 0.001$ ) and increased wall thickness ( $p \leq 0.004$ ) independently predict mortality
<i>Adults</i>				
Barbaro/GISCA/1998 <sup>4</sup>	952	Asymptomatic patients with HIV infection	5	8% dilated cardiomyopathy over 60 months. Mean annual incidence 15.9 cases/1000 patients. Dilated cardiomyopathy associated with decreased CD4 count and zidovudine use
Heidenreich/1995 <sup>15</sup>	231	HIV infected adults	5	Pericardial effusion 11%/year in AIDS patients. Survival of AIDS patients with effusion 36% at 6 months compared with 93% at 6 months in those without effusion
Currie/1994 <sup>16</sup>	296	HIV infected adults mean age 32.7 years	4	Dilated cardiomyopathy associated with low CD4 count. Significantly decreased survival in those with dilated cardiomyopathy compared to those with normal hearts at similar infection stage



Figure 1 Necropsy finding of dilated cardiomyopathy in a patient who died of AIDS. There is remarkable dilatation of the left ventricular cavity with slight myocardial hypertrophy.

their surfaces for extended time periods and may chronically release cytotoxic cytokines (tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), endothelin-1 (ET-1)) contributing to progressive and late tissue damage in both systems independently of HAART.<sup>9</sup>

#### Coronary artery disease

Accelerated coronary artery disease in HIV infected patients may result from atherogenesis stimulated by virus infected monocyte-macrophages, possibly caused by altered leucocyte adhesion or arteritis.<sup>10</sup> Coronary artery disease is observed with increasing frequency among HIV patients receiving protease inhibitors in the ambit of HAART.<sup>1</sup> Despite the clinical benefits of protease inhibitors, complications such as lipodystrophy, insulin resistance, and high concentrations of low density lipoprotein and triglycerides have been described in up to 60% of patients treated with HAART regimens.<sup>2,11</sup> In 10–20% of patients, these alterations of metabolism have severe manifestations.<sup>2,11</sup> Effects of pre-existing cardiovascular risk factors combined with atherogenic effects of current drug treatments for HIV infection appear to result in an increase in acute coronary syndromes, even in young HIV infected individuals.

It may be important to consider traditional coronary risk profiles and to alter those that can be modified in the evaluation and continued treatment of patients for HAART. Diet and exercise should not be overlooked, because both can be effective in managing these complications without causing further side effects.<sup>11</sup> Fibric acid derivatives and statins can lower HIV associated cholesterol and triglyceride concentrations, although further data are needed on interactions between statins and protease inhibitors.<sup>11,12</sup> Lovastatin should be avoided in patients receiving concomitant drugs that may potentiate skeletal muscle toxicity with this agent.<sup>13</sup> Hypoglycaemic agents may have some role in managing glucose abnormalities, although troglitazone cannot be recommended for fat abnormalities alone and metformin may cause lactic acidosis.<sup>12</sup> Perhaps a better understanding of protease inhibitors' effects on lipid and metabolic pathways will lead to a new generation of drug treatments without metabolic alterations. This understanding may also lead to new treatments for dyslipidaemias and alterations of metabolism unrelated to HIV infection.



Figure 2 Necropsy finding of *Candida albicans* endocarditis in an AIDS intravenous heroin user. Note the thrombotic formation on the closing edge of the posterior leaflet of the tricuspid valve (arrow) going down to the right ventricular cavity and involving the chordae tendineae.

#### HIV associated pulmonary hypertension and right ventricular dysfunction

The incidence of HIV associated pulmonary hypertension is estimated to be 1/200, much higher than the 1/200 000 found in the general population.<sup>1</sup> Primary pulmonary hypertension is estimated to occur in about 0.5% of hospitalised AIDS patients and is a cause of severe cardiac impairment with associated cor pulmonale and death.<sup>1</sup> The pathogenesis is multifactorial and poorly understood. HIV may cause endothelial damage and mediator related vasoconstriction through stimulation by the envelope glycoprotein 120, including direct release and pulmonary vasoconstrictor effects of ET-1, IL-6 and TNF- $\alpha$ . HIV is frequently identified in alveolar macrophages on histology.<sup>1,14</sup> These macrophages release TNF- $\alpha$ , oxide anions, and proteolytic enzymes in response to infection. Effects of HAART on pulmonary artery endothelial cells are unknown.

#### Endocarditis

The prevalence of infective endocarditis in HIV infected patients is similar to that of patients of similar behaviour risk—that is, intravenous drug use.<sup>1</sup> Estimates of endocarditis occurrence vary from 6.3–34% of HIV infected patients who use intravenous drugs.<sup>1,5</sup> Right sided valves are predominantly affected<sup>5</sup> (fig 2).<sup>1</sup> Patients with and without HIV generally have similar presentation and survival rates from infective endocarditis. However, patients with late stage HIV disease have higher mortality from infective endocarditis than do asymptomatic HIV infected patients.<sup>1</sup> As the autoimmune response to bacterial endocarditis is often largely responsible for associated valvar destruction, HIV infected patients may have an altered course. For example, HIV infected patients have a higher risk of developing salmonella endocarditis than immunocompetent patients because they are more likely to develop salmonella bacteraemia during salmonella infection. However, they respond better to antibiotic treatment and may be less likely to sustain valvar damage because of impaired immune function.<sup>1</sup>

#### Pericardial effusion

The prevalence of pericardial effusion in asymptomatic HIV infected patients is estimated at 22%.<sup>15</sup> Pericardial effusion in HIV disease may be related to opportunistic infections (fig 3) or to malignancy, but most often a clear aetiology is not found.<sup>15</sup> The effusion may be part of a generalised serous effusive process also involving pleural and peritoneal surfaces. This “capillary leak” syndrome is likely

