

# How does HIV/AIDS cause cardiomyopathy?

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*HIV/AIDS-related cardiomyopathy is a relatively recent concern. Only in the last decade, thanks to anti-retroviral therapy, have human immunodeficiency virus type 1 (HIV 1) infection and acquired immunodeficiency syndrome (AIDS) become chronic, at least in the developed world. For this reason, and because of confounding factors (comorbidity, the iatrogenic impact of nucleoside reverse transcriptase inhibitors) and widely differing study populations, some major issues remain unresolved: the prevalence of cardiomyopathy in HIV infection (figures range from zero to 10%), the cellular target of HIV (cardiomyocytes lack CD4 receptors), and the specific impact, if any, of cardiac HIV infection. However, there is now strong evidence, found in around half of autopsy cases, that underlying the cardiomyopathy is a myocarditis resulting from interaction between cytokines and HIV structural proteins.*

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**A**cquired immunodeficiency syndrome (AIDS) was first described in 1981,<sup>1</sup> but its etiological agent was not identified as the human immunodeficiency virus type 1 (HIV-1) until 1983-1984. At that point, the virus that came to be known commonly as HIV was characterized,<sup>2,3</sup> and a deeper appreciation of key elements of the syndrome of AIDS became available. Infection with HIV, the primary retrovirus responsible for AIDS, occurs as a result of exposure to infected body fluids through sexual, parenteral (blood, blood products, illicit injection drugs, occupational injury), or vertical transmission (mother to fetus).

## WHAT IS THE SCOPE OF HIV/AIDS HEART DISEASE?

To put the AIDS epidemic in perspective, more than 40 million people worldwide were infected with HIV as of 2005, and more than 20 million have died since the epidemic began.<sup>4</sup> Most deaths occurred in sub-Saharan Africa, where over 13 million children have been orphaned. In the United States, over 1 million people are now "HIV positive" (infected with HIV based on virological testing<sup>5</sup>), although not all have AIDS. In the developed world, the HIV infection rate is rising in eastern Europe.<sup>6</sup>

Because of the severe effects of immunodeficiency in AIDS, the course of untreated illness was rapidly

fatal in the early days of epidemic. This resulted in part from unfamiliarity with the condition and lack of effective therapy to treat HIV infection. Unfortunately, today many of those same problems persist in resource-poor areas where the diagnosis of HIV/AIDS may be made late in the disease and where antiretroviral therapy is not yet available.

Justifiably, in the early days of the epidemic, heart disease in the setting of HIV/AIDS was not considered a critical clinical consideration. More urgent clinical problems were abundant and eclipsed all others. The advent of widespread use of antiretroviral therapy for HIV/AIDS in the developed world, coupled with guidelines for antiretroviral treatment from the Center for Disease Control (CDC), has contributed

### SELECTED ABBREVIATIONS

<b>AIDS</b>	acquired immune deficiency syndrome
<b>AZT</b>	azidothymidine = zidovudine
<b>CHF</b>	congestive heart failure
<b>CM</b>	cardiomyopathy
<b>HAART</b>	highly active antiretroviral therapy
<b>HIV</b>	human immunodeficiency virus
<b>mtDNA</b>	mitochondrial deoxyribonucleic acid
<b>NRTI</b>	nucleotide reverse transcriptase inhibitor
<b>SIV</b>	simian immunodeficiency virus

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greatly to prolongation of productive life and has led to initiating similar approaches in parts of the developing world.<sup>7</sup> As a consequence of more effective treatment and care for patients with HIV/AIDS, longevity with HIV/AIDS has added to the clinical spectrum of diseases referable to the various organ systems. Thus, in the last decade of the epidemic (at least in the developed world) HIV/AIDS has taken on the behavior of a chronic illness that requires continuous monitoring and therapy (analogous to diabetes mellitus).

The role of heart disease (specifically cardiomyopathy [CM]) in HIV/AIDS patients in the developing world may be somewhat different and has only recently been addressed more extensively.<sup>8-14</sup> Because a variety of cardiovascular illnesses may be intersecting in that population,<sup>15</sup> heart disease from HIV/AIDS may not be as pressing as other more common cardiovascular illnesses. This review primarily addresses HIV/AIDS in the developed world. It should be understood that improvements in therapy and survival occurring in patients with HIV/AIDS throughout the world may make points discussed here applicable to other geographic locales.

**HAS AIDS  
CARDIOMYOPATHY  
EVOLVED WITH HIV/AIDS?**

As alluded to above, early in the HIV/AIDS epidemic, the heart was recognized as an authentic target of disease,<sup>16</sup> but significant clinical cardiac involvement was unusual (or not reported) based on the profound effects of opportunistic infection, respiratory failure, wasting, and Kaposi's sarcoma, which were more prevalent and life-threatening, and which more accurately characterized this relatively new clinical

entity. Although HIV is etiologically linked to AIDS per se, controversy persists regarding the prevalence of myocardial infection with HIV (or related pathogens), the cellular target for HIV infection within the heart, and the clinical impact, if any, of HIV infection in that target organ. All of these important points led to attempts at identifying the pathogenetic role (if any) of HIV infection of the myocardium in HIV/AIDS CM.

Autopsy findings from studies performed early in the epidemic defined many pathological features, but focused predominantly on other organs.<sup>17</sup> Cardiac effects, where demonstrated, appeared frequently as accompanying findings. A series of papers examined postmortem findings in HIV/AIDS that particularly focused on the cardiovascular system.<sup>16,18-20</sup> Incidence of cardiac involvement at autopsy varied, appeared dependent on the pathological and clinical definitions and criteria applied to the cases. Findings varied somewhat based on epidemiological features among the different populations of HIV/AIDS patients in different settings within the developed world. Although it was understood that most autopsy studies from the United States came from urban, academic medical centers, the demographics followed closely the patient populations of the particular geographic location, which were somewhat unique. For example, some of the autopsy studies included a significant number of patients who were intravenous drug abusers; others included a predominantly homosexual male population, and so on. Female patients were relatively few in most of the earlier studies.

This simple, but important, demographic factor created some gaps in understanding the global concept of HIV/AIDS CM. Frequently, distinct

patterns of illnesses could be found in some populations. Ultimately, that demographic artifact could skew the interpretation of those data when applied to other populations. Moreover, it may be reasonable to suggest comorbid conditions impact the cardiovascular health of patients with AIDS and may thus impact cardiac performance and development of HIV/AIDS CM, and these also could impact results. This latter point becomes increasingly reasonable with the advent of antiretroviral therapy, and the role of comorbid conditions must be ascertained in HIV/AIDS CM cases<sup>21</sup> and must be considered in all studies that are population-based in a given locale.

When CM in HIV/AIDS was reported in 1986,<sup>22</sup> the index patient received no antiretroviral therapy. Additional CM cases in HIV/AIDS were reported subsequently.<sup>23</sup> The prevalence of CM in HIV/AIDS appeared to be increasing, but ranged  $\approx 10\%$  or less based on autopsy findings in the developed world and unpublished data. A 1-year consecutive enrollment study of patients admitted to the intensive care unit in an urban center revealed 6% of admissions with either HIV-1 infection or HIV/AIDS had echocardiographically-documented CM. Mortality was 25%.<sup>24</sup>

Persistent echocardiographic abnormalities in HIV/AIDS were considered ominous predictors of CM, but other changes were reversible and thus considered less serious.<sup>25</sup> In Britain, 13 of 173 HIV/AIDS patients had CM as a correlate of advanced HIV-1 disease. Data indicated no correlation between HIV/AIDS CM and other potential causes of CM, myocarditis, zidovudine (= azidothymidine, AZT) treatment, or infection with cytomegalovirus or *T gondii*.<sup>26</sup> In hemophiliacs, 2 of 27 patients



with HIV-1 infection had echocardiographically documented CM.<sup>27</sup> Recent data from intensive care settings in the United States point to increased admissions with cardiovascular disease and HIV/AIDS and declining admissions with respiratory failure in that setting.<sup>28,29</sup>

Contrasting data come from other European centers. The direct effect of HIV/AIDS on the development of "heart disease" was evaluated in a report from Scandinavia in a population of HIV/AIDS patients without opportunistic infections.<sup>30</sup> According to echocardiography, no patient had significant pericardial effusions, cardiac tumors, endocarditis, or CM. In a subgroup that died of AIDS, HIV was not a myocardial pathogen. Other studies suggested that myocardial filling and relaxation abnormalities are important in HIV infection.<sup>31</sup> From these points, it may be inferred that the pathogenetic or etiological ties between HIV and CM in HIV/AIDS were not strong.

### **DOES HIV INFECT THE MYOCARDIUM, AND IF SO HOW?**

One reasonable hypothesis to explain CM in HIV/AIDS is to consider HIV itself a cardiac pathogen. HIV gains entry into cells through binding between its envelope glycoprotein group 120 (gp120) and CD4 receptors found on specific lymphocytes, including helper T cells, and macrophages and dendritic cells. Unfortunately, the fact that cardiac myocytes lack CD4 receptors creates a conundrum for understanding of the pathogenetic mechanisms of CM in HIV/AIDS. Evidence proving that HIV enters human cardiac myocytes is less compelling and more circumstantial. This weakens a pathogenetic link between HIV/AIDS and the development of CM and myocarditis in patients.

Pathological studies from our group<sup>32</sup> and others<sup>33</sup> addressed the question of whether HIV served as an infectious agent in the human myocardium. They documented HIV infection in pathological sections of myocardium in patients with HIV/AIDS. The *in situ* hybridization techniques offered the relatively unique advantage of preserved histologic architecture and precise localization of HIV sequences within particular tissue (eg, heart).

The major technical shortcoming was that *in situ* hybridization as performed in those studies could not unambiguously identify cell type (ie, myocyte vs nonmyocyte). Nonetheless, data from our study<sup>32</sup> indicated over 20% autopsy heart samples exhibited HIV infection. The abundance of signal was small and HIV infection in the heart neither correlated with clinical evidence of CM, nor was cytological identity of the infected cell ascertained based on the limitations alluded to above.

Convincing experimental data from simian immunodeficiency virus (SIV) studies in nonhuman primates clarified some of the ambiguities. Although *in vivo* models of HIV/AIDS are generally limited in many ways,<sup>34</sup> SIV is an authentic model of HIV/AIDS, and thus may serve as a model of CM and myocarditis in HIV/AIDS. Unfortunately, primate studies are limited in number because of logistic difficulties, ethical considerations, and so on. Despite this, data from Shannon's group and others suggest SIV (and thus HIV) is harbored in the nonmyocyte pool of myocardial cells, instead of the cardiomyocytes.<sup>35-38</sup> The studies further point out that CM in the simian model of HIV/AIDS is a chronic condition, that infection with retrovirus is targeted to the nonmyocyte pool, and that clinical events correlate with severity of infection and injury.

Taken together, these important experimental issues tie inflammation of the heart to CM in HIV/AIDS.

### **WHAT IS THE ROLE OF MYOCARDITIS IN HIV/AIDS CM?**

Myocarditis in HIV/AIDS has varying prevalence in the reports over the decades. However, myocarditis could provide a rational explanation for the development of CM in HIV/AIDS. Variability was apparent. A Scandinavian study of 60 consecutive autopsies revealed 42% prevalence,<sup>30</sup> while in Southern California, a 74% prevalence was described,<sup>39</sup> and in 100 autopsies from Puerto Rico, changes in the heart occurred in 32% of cases. In Reilly's post-mortem review,<sup>40</sup> 26 of 58 samples satisfied the Dallas criteria for myocarditis with clinical correlation, and lymphocytic infiltrates were found more commonly early in the HIV/AIDS epidemic.<sup>20,41</sup>

As mentioned, the prevalence of inflammatory infiltrates in the heart of patients with HIV/AIDS varied substantially in early studies and the relationship of the identified infiltrates to either cardiac dysfunction or HIV infection in the heart were similarly tenuous. Findings at UCLA indicated less than 10% prevalence of bona fide myocarditis from autopsy samples of myocardium. Other investigators in the United States and elsewhere found significantly higher prevalence of inflammatory infiltrates in the heart. Data from large studies performed in Italy putatively corroborated high prevalence of AIDS CM and significant cardiac infection with HIV in HIV/AIDS patients.<sup>42,43</sup> However, those papers were retracted editorially.<sup>44,45</sup> This unfortunate series of events further obfuscated the diagnosis and treatment of myocarditis and of CM in HIV/AIDS.

### WHAT IS THE ROLE OF CYTOKINES IN CM IN HIV/AIDS?

Because cytokines play key roles in AIDS,<sup>46</sup> and in cardiac dysfunction and congestive heart failure (CHF) in the broader sense,<sup>47</sup> it is reasonable to consider that circulating or locally acting cytokines may be involved pathogenetically or pathophysiologically in CM in HIV/AIDS. Cytokines that are reasonable candidates for impacting cardiac function in HIV/AIDS include endothelin (particularly ET-1) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ).<sup>48</sup> Left ventricle expression of atrial natriuretic factor (ANF), a marker of left ventricle hypertrophy, cardiac dysfunction and remodeling, and reversion to an embryologically earlier genetic program,<sup>49</sup> may also be important diagnostically and prognostically.<sup>50</sup> Based on information from the numerous studies of CHF unrelated to HIV/AIDS and from studies of HIV/AIDS in absence of cardiovascular disease, substantial information has been obtained regarding the role of cytokines and the potential interaction of cytokines with HIV structural proteins in the pathogenesis of AIDS CM. Finkel's group demonstrated that HIV envelope gp120 induces nitric oxide production through inducible nitric oxide synthase in vitro and that p38 MAP kinase is mechanistically involved in cardiac dysfunction.<sup>51-53</sup> Other investigators suggested that reactive nitrogen species may be critical pathophysiologically.<sup>54</sup> Some evidence links gp120 to HIV/AIDS and CM both in human samples and those from primates, and may serve as the link between primate findings in vivo and clinical data.<sup>55</sup> Taken together, these points may offer a plausible relationship between the pathogenesis of CM in patients with HIV/AIDS and in patients who are not infected.

### DOES ANTIRETROVIRAL THERAPY IMPACT CM IN HIV/AIDS?

Despite new antiretroviral agents being developed<sup>56</sup> and some promise from HIV vaccine studies,<sup>57</sup> HIV/AIDS remains a major clinical threat. Treatment approaches were developed as early as the mid-1980s and focused on stopping viral replication. The earliest successful group of antiretroviral drugs came from a class called nucleoside reverse transcriptase inhibitors (NRTIs), which are pharmacological analogs that mimic native nucleosides used for DNA replication. Today, in combinations of highly active antiretroviral therapy (HAART), NRTIs are cornerstones of AIDS therapy in the developed world. Moreover, HAART containing NRTIs is being brought to some areas in the developing world in heroic efforts.<sup>58-60</sup>

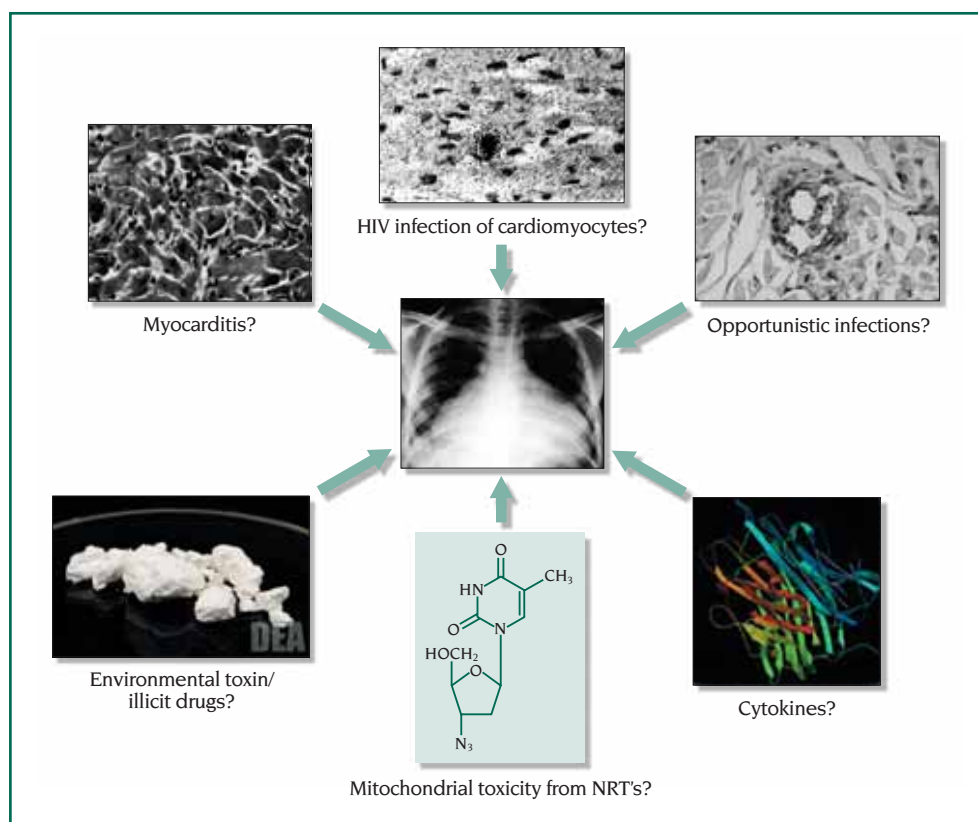
Shortly after NRTIs became efficacious in the developed world, NRTI side effects were noted in patients. In particular, HIV/AIDS patients that received relatively high-dose therapy, particularly AZT, experienced a disabling skeletal muscle myopathy that resembled some relatively rare mitochondrial genetic diseases. Although earlier data existed from studies in vitro that suggested the possibility of toxicity from NRTIs,<sup>61</sup> data from those studies were not extrapolated to clinical situations.

A series of seminal clinical observations,<sup>62,63</sup> a group of related experimental studies,<sup>64-66</sup> tragic results in a clinical trial with a NRTI for hepatitis B infection,<sup>67</sup> and related in vitro and in vivo studies<sup>68-70</sup> shed light on mechanisms of NRTI toxicity. It was demonstrated that AZT toxicity in humans was related mechanistically to mitochondrial dysfunction, particularly inhibition

of mitochondrial (mt) DNA replication in vitro by active AZT triphosphate.<sup>71</sup> Those data were correlated with data from studies in vivo of NRTI toxicity to heart muscle in rats, mice, woodchucks, and other species.<sup>65,66,72</sup> A "DNA pol- $\gamma$  hypothesis"<sup>73</sup> was generated and evolved into the "mitochondrial dysfunction hypothesis"<sup>74</sup> that expands its original scope. At present, NRTI toxicity encompasses defective mtDNA replication, alteration of intramitochondrial and intracellular processing of NRTIs,<sup>75</sup> related defects from oxidative stress, and genetic defects of the mitochondrial genome.<sup>76</sup>

The cornerstones of the concept of acquired mitochondrial dysfunction are energy deprivation secondary to mtDNA depletion,<sup>66</sup> *mitochondrial oxidative stress* from ineffective utilization of electron transport,<sup>77-80</sup> and *mtDNA mutations* that may result from oxidative mtDNA damage<sup>81</sup> or from mutagenic changes from NRTIs per se. The current prevailing theory suggests that it is eminently reasonable to consider AZT-induced mitochondrial toxicity to involve defective mtDNA replication (reviewed in 74,82-84), but it should be noted that the hypothesis is neither proven clinically nor accepted universally.<sup>85</sup> Importantly, the cellular locus at which the pathophysiological defect occurs may require further investigation.<sup>86</sup>

In the earlier experimental studies, decreased mtDNA, mtRNA, mitochondrial polypeptides, and defective mitochondrial ultrastructure, correlate with micromolar, mixed Kis for dideoxy-NRTI triphosphates with pol  $\gamma$ . Intriguing recent data from patients suggest that genetic differences in either the mtDNA "template,"<sup>87</sup> in the enzymatic and structural machinery of the mitochondrial DNA replicon, or in en-



**Figure 1.** Overview of possible etiologies and pathogenesis for acquired immunodeficiency syndrome cardiomyopathy (AIDS CM). Clockwise from top left: inflammatory heart disease occurs in HIV/AIDS, but with varying prevalence; Human immunodeficiency virus (HIV) itself infects the heart, albeit with low infectivity; early in the epidemic, and before antiretroviral therapy, opportunistic infections (like *Cryptococcus species*<sup>93</sup>) were common and could cause CM; cytokines like tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) can contribute to cardiac dysfunction in HIV/AIDS; azidothymidine (AZT) and other nucleoside reverse transcriptase inhibitors (NRTIs) are potent toxins to mitochondrial (mt) DNA replication *in vivo*; drugs like cocaine can affect the heart through effects on adrenergic signaling and other means. Each contributes to the development of CM in various settings where HIV/AIDS may be prevalent.

zymes and transporters that maintain nucleotide precursor pools<sup>88</sup> each may impact mitochondrial dysfunction.

### WHERE DOES OPPORTUNISTIC INFECTION FIT IN HIV/AIDS CM?

Immune-compromised patients are vulnerable to a variety of infections. Opportunistic infections of the heart in patients with AIDS have been documented anatomically in the pericardium, myocardium, and endocardium, but again the prevalence has changed as the epidemic is into the 3rd decade. Among the documented cardiac infections include: *T gondii*,<sup>89-92</sup> *Cryptococcus species*,<sup>93</sup> CMV,<sup>94-96</sup> *Candida*,<sup>97,98</sup> disseminated *P carinii*,<sup>99,100</sup> atypical mycobacteria,<sup>101</sup> *Aspergillus*,<sup>102</sup> *T cruzi*,<sup>103,104</sup> and *Microsporidium*.<sup>100</sup> Irrespective of the infectious agent, it is clear today that in the devel-

oped world the effects of metabolic syndrome and mitochondrial dysfunction from HAART outweigh any of the risks described earlier in the epidemic.

### WHAT ROLE DO ILLICIT DRUGS PLAY IN CM IN HIV/AIDS?

Because risk behaviors for HIV/AIDS infection may be associated with other risk behaviors, illicit drugs may be associated with HIV/AIDS. In the developed world, intravenous drug abuse is a significant risk behavior associated with HIV/AIDS. It is possible that such behavioral risk factors could also confound a pathogenetic relationship between AIDS and myocarditis. It may be reasonable to consider the relative contributions of both HIV/AIDS and conditions related to its attendant risk behaviors (such as infective endocarditis and intravenous

drug abuse) in consideration of HIV/AIDS CM. Abuse of known cardiotoxins (eg, cocaine<sup>105</sup> or alcohol<sup>106</sup>) can contribute to the development of heart failure in HIV/AIDS and to the development of CM, since CM from those toxins can occur independent of HIV/AIDS exposure. Importantly, cocaine has been documented as a cause of CM, which occasionally has been reported to be reversible.<sup>107</sup> The role of other nonprescription drugs and home remedies in the development of CM in HIV/AIDS may become more important in the future.

Figure 1 gives an overview of the above etiologies for CM in HIV/AIDS.

### WHERE DOES CM IN HIV/AIDS GO FROM HERE?

It is abundantly clear that CM in HIV/AIDS, like the disease itself, has undergone some remarkable

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changes over the 20 years since the first case was documented. Clearly, the nature and role of inflammatory heart disease, cytokines acting locally and systemically, nutritional status, illicit drugs, and therapeutic side effects have played a role in this period. As we approach the next, and hopefully the last decade of HIV/AIDS epidemic, host genetics at the pharmacological and toxicological levels likely will have greater impact on both clinical decision-making and on the course of disease for individuals and populations infected with HIV and with CM in HIV/AIDS.<sup>108-111</sup>

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