Risk of Heart Failure With Human Immunodeficiency Virus in the Absence of Prior Diagnosis of Coronary Heart Disease

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Background: Whether human immunodeficiency virus (HIV) infection is a risk factor for heart failure (HF) is not clear. The presence of coronary heart disease and alcohol consumption in this population may confound this association.

Methods: To determine whether HIV infection is a risk factor for incident HF, we conducted a population-based, retrospective cohort study of HIV-infected and HIV-uninfected veterans enrolled in the Veterans Aging Cohort Study Virtual Cohort (VACS-VC) and the 1999 Large Health Study of Veteran Enrollees (LHS) from January 1, 2000, to July 31, 2007.

Results: There were 8486 participants (28.2% HIV-infected) enrolled in the VACS-VC who also participated in the 1999 LHS. During the median 7.3 years of follow-up, 286 incident HF events occurred. Age- and race/ethnicity–adjusted HF rates among HIV-infected and HIV-uninfected veterans were 7.12 (95% confidence interval [CI], 6.90–7.34) and 4.82 (95% CI, 4.72–4.91) per 1000 person-years, respectively. Compared with HIV-uninfected veterans, those who were HIV infected had an increased risk of HF (adjusted hazard ratio [HR], 1.81; 95% CI, 1.39–2.36). This association persisted among veterans who did not have a coronary heart disease event or a diagnosis related to alcohol abuse or dependence before the incident HF event (adjusted HR, 1.96; 95% CI, 1.29–2.98). Compared with HIV-uninfected veterans, those who were HIV infected with a baseline Human immunodeficiency virus 1 (HIV-1) RNA level of 500 or more copies/mL had a higher risk of HF (adjusted HR, 2.28; 95% CI, 1.57–3.32), while those with baseline and a recent HIV-1 RNA level less than 500 copies/mL did not (adjusted HR, 1.10; 95% CI, 0.64–1.89; P < .001 for comparison between high and low HIV-1 RNA groups).

Conclusions: Our data suggest that HIV infection is a risk factor for HF. Ongoing viral replication is associated with a higher risk of developing HF.

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fection and possible effects of HIV infection and antiretroviral therapy on body habitus and metabolic factors, it is important to understand the associations of established and novel risk factors and define the role of HIV itself in the risk of HF. An understanding of risk factors is critical in designing targeted intervention strategies to reduce such risk and improve cardiovascular clinical outcomes in this population. The objective of this study, therefore, was to determine whether HIV infection was independently associated with an increased risk of incident HF. We performed additional analyses in patients without a prior CHD event or alcohol abuse or dependence diagnosis before developing HF and assessed the association between suppressed HIV-1 RNA viral loads and HF to further understand the impact of HIV itself on the risk of HF.

METHODS

We conducted a population-based, retrospective cohort study combining 2 established data sources: the Veterans Aging Cohort Study Virtual Cohort (VACS-VC) and the 1999 Large Health Study of Veteran Enrollees (LHS). The VACS-VC is a cohort of individuals with or without HIV infection matched on age, sex, race/ethnicity, and clinical site who were identified from the US Department of Veterans Affairs (VA) administrative data in the fiscal years 1998-2003. This cohort has been described and used for studies of clinical outcomes in the HIV-infected and HIV-uninfected veteran population. Briefly, the cohort consists of extensive clinical, laboratory, and pharmacy data from the Immunology Case Registry, the Pharmacy Benefits Management database, the Decision Support System database, and the National Patient Care Database. The 1999 LHS was a survey administered between June 1999 and January 2000 designed to assess the health status of veterans. The institutional review boards at the University of Pittsburgh, Yale University, and the West Haven VA Medical Center approved this study.

All participants in the VACS-VC/LHS were eligible for the present study. We excluded those with prevalent CHD, angina, or HF at baseline (n = 3209). We also excluded patients who were diagnosed as having cancer (except nonmelanoma skin cancer [n = 1716]) to increase the possibility of adequate length of survival to develop an HF event during the follow-up period and to remove any possible bias resulting from the use of some antineoplastic drugs that are cardiotoxic; women were excluded because of the small number (n = 276).

DEFINITIONS

Infection with HIV was defined as 1 or more inpatient and/or 2 or more outpatient International Classification of Diseases, Ninth Revision (ICD-9) codes for HIV infection confirmed by the participant’s presence in the VA Immunology Case Registry. Hepatitis C virus infection was defined as a positive result of a hepatitis C virus antibody test or 1 or more inpatient and/or 2 or more outpatient ICD-9 codes for this diagnosis. These definitions have been used in multiple studies and have been found to correlate well with medical record reviews and/or laboratory test–based diagnoses. We used the presence of 1 or more inpatient and/or 2 or more outpatient ICD-9 codes to identify CHD (ICD-9 codes 410 and 411) events and HF (ICD-9 codes 425 and 428). The ICD-9 codes for various cardiovascular diagnoses are highly predictive of actual adjudicated clinical diagnoses. The positive predictive values of ICD-9 codes for HF, myocardial infarction, cerebrovascular disease, and diabetes mellitus are 94.3%, 81.9%, 89.4%, and 96.2%, respectively.

We selected these codes on the basis of prior studies within the VA health care system and because these definitions had high agreement with the formal adjudication process within the Cardiovascular Health Study. Hypertension was also defined using ICD-9 codes (401, 401.1, 401.9, 402, 402.1, 402.11, 402.9, 403, 404, 404.1, 404.9, 405, 405.1, 405.11, 405.19, 405.9, 405.91, 405.99, and 437.2). Diabetes and dyslipidemia were diagnosed according to our previously published algorithms using a combination of laboratory measurements, medication prescriptions, and ICD-9 codes. Self-reported height and weight were used to calculate body mass index (calculated as weight in kilograms divided by height in meters squared). Self-reported data on smoking were obtained from the LHS survey and categorized as history of current smoking, past smoking, or never smoking. History of cocaine abuse or dependence was defined using ICD-9 codes (304.20-304.23 and 305.6-305.63). History of alcohol abuse or dependence was defined using ICD-9 codes based on previous work in the VACS.

Among the HIV-infected patients, we collected data on baseline CD4+ lymphocyte counts, HIV-1 RNA levels, and use of combination antiretroviral therapy (CART). Baseline CD4+ lymphocyte count and HIV-1 RNA level measurements were from 180 days before and up to 180 days after the time of enrollment in the LHS, and recent measurements were the CD4+ lymphocyte count and HIV-1 RNA level determined closest to the date of the incident HF event, death, or last follow-up observation. Baseline CART was defined as receipt of 3 or more antiretroviral agents for 30 or more days at time of enrollment into the study. Patients who had not received CART at time of enrollment through their last observation date or censor date were considered CART naive. Because CART data were available only through June 2005, the analyses involving CART-naive participants were truncated to 2005. Follow-up time was time to an HF event, death, or last known visit within the VA health care system during the study period. We confirmed deaths using the VA vitals status file, the Social Security Administration death master file, the Beneficiary Identification and Records Locator Subsystem, and the Veterans Health Administration’s medical SAS inpatient data sets.

STATISTICAL METHODS

Descriptive statistics for all variables by HIV status were assessed using t test or its nonparametric counterpart for continuous variables and χ² test or Fisher exact test for categorical variables. Cox proportional hazards models were used to estimate the hazard ratio (HR) and 95% confidence intervals (CIs) for incident HF associated with HIV infection vs noninfection after adjusting for confounders. The proportional hazards assumption was assessed using the Grambsch-Therneau method. Additional analyses were performed to determine whether the association between HIV infection and HF persisted after excluding patients who had a diagnosis of alcohol abuse or dependence before the development of the incident HF event during the follow-up period. Secondary analyses also examined the association between HIV status and HF stratified by HIV-1 RNA level, CD4+ lymphocyte count, and antiretroviral therapy status. To explore the impact of viral suppression, we compared HIV-uninfected participants with HIV-infected participants who had baseline and recent HIV-1 RNA levels less than 500 copies/mL, baseline but not recent HIV-1 RNA levels of less than 500 copies/mL, and those with baseline HIV-1 RNA levels of 500 or more copies/mL. Additional analysis included interaction terms between HIV status and individual comorbidities. None of these factors were found to be statistically significant and they are not presented here.
Between January 1, 2000, and July 31, 2007, a total of 8486 patients met our criteria for inclusion, of whom 2391 (28.2%) were HIV infected and 6095 (71.8%) were HIV uninfected (Table 1). The median duration of follow-up was 7.3 years (range, 0.01-7.48 years) for the entire cohort. There were 286 incident HF events and 1096 deaths during the follow-up period. Among patients who did not develop HF or die (n=7104), 87.1% completed follow-up to within 1 year of the end of the follow-up period.

The median age was 48.0 years in both groups. Participants with HIV infection were more likely to have hepatitis C virus coinfection (30.5% vs 11.4%) and cocaine abuse or dependence (21.9% vs 15.7%) and higher reported rate of current smoking (55.0% vs 45.3%), but were less likely to have hypertension (18.7% vs 28.8%) or diabetes (16.7% vs 24.8%) (P <.001 for all comparisons). The proportion of subjects with dyslipidemia or a diagnosis of alcohol abuse or dependence was similar in both groups. Patients with HIV infection had a lower mean (SD) body mass index compared with those without HIV infection (25.1 [4.2] vs 28.1 [5.3]).

The age- and race/ethnicity–adjusted rates of incident HF were 7.12 per 1000 person-years (95% CI, 6.90-7.34) for HIV-infected patients and 4.82 per 1000 person-years (95% CI, 4.72-4.91) for HIV-uninfected patients. Compared with HIV-uninfected patients, HIV-infected patients had a significantly increased risk of HF after adjusting for traditional risk factors (HR, 1.81; 95% CI, 1.39-2.36; Table 2 and Figure 1). Other factors significantly and positively associated with a risk of HF were increasing age, African American race, current smoking, body mass index greater than 30, hypertension, diabetes, and a diagnosis of alcohol abuse or dependence. Compared with patients without HIV infection, those with HIV infection who had baseline HIV-1 RNA levels of 500 or more copies/mL had a significantly higher risk of HF (adjusted HR, 2.28; 95% CI, 1.57-3.32). Those with HIV infection who had baseline and recent HIV-1 RNA levels less than 500 copies/mL, however, did not have an increased risk of HF (adjusted HR, 1.10; 95% CI, 0.64-1.89). The difference between the low HIV-1 RNA and high HIV-1 RNA group was statistically significant (P < .001) (Table 2).

Although all participants in our study did not have CHD, HF, or angina at the time of enrollment, we conducted additional analyses excluding patients who developed CHD during the follow-up period prior to the diagnosis of HF, had a diagnosis of alcohol abuse or dependence, or both (Table 3 and Figure 2). Among patients without a CHD event prior to the diagnosis of HF, the association between HIV infection and HF persisted (HR, 1.92; 95% CI, 1.42-2.61). Similarly, among patients who did not have a diagnosis of alcohol abuse or dependence at baseline or during the follow-up period, HIV infection remained significantly associated with an
Our data suggest that HIV infection is associated with an increased risk of HF after adjusting for traditional CHD risk factors. This risk persisted even after restricting the sample to patients who did not have a diagnosis of CHD, HF, or angina at baseline or a diagnosis of CHD during the follow-up period prior to the diagnosis of HF, a diagnosis of alcohol abuse/dependence, or both. Ongoing viral replication (HIV-1 RNA level $\geq 500$ copies/mL) was associated with a higher risk of developing HF. However, HIV-infected participants with baseline and recent HIV-1 RNA level less than 500 copies/mL did not have an increased risk of HF compared with HIV-uninfected participants.

To our knowledge, there are no definitive studies on the risk of HF that compared HIV-infected with HIV-uninfected people who are free of baseline CHD. Diastolic dysfunction has been reported in 48% to 50% of HIV-infected persons, but the proportion of this dysfunction attributable to preexisting CHD is not known.29-31 Myocarditis is present in up to half of patients with AIDS in autopsy studies,32,33 but overt antemortem HF or autopsy evidence of ventricular dysfunction is not present in all such cases. In addition, these smaller studies are from the pre-CART era and lack HIV-uninfected controls to determine a direct association with HIV infection. In contrast, one study3 of 91 HIV-infected participants did not find any significant evidence of right or left ventricular dysfunction as measured by radionuclide ventriculography. To our knowledge, our study is the largest to investigate the relationship between HF and HIV infection and the first to demonstrate such an association and provide evidence of HIV infection as an independent risk factor for HF.

Although the exact mechanism by which HIV infection is associated with HF is not well understood, several possible mechanisms exist, including direct effects of the HIV, comorbidities associated with HIV infection (eg, heavy alcohol consumption), antiretroviral therapy leading to an increased risk of CHD and subsequent HF, nutritional deficiencies, and immunologic damage to the myocardium. Our results suggest that HIV itself is playing an important and independent role. Even after excluding patients with a baseline history of CHD, HF, and angina, as well as a CHD event in the follow-up period prior to the diagnosis of HF and a history of alcohol abuse or dependence diagnosis, the risk of incident HF was still substantial among the HIV-infected cohort. Ongoing HIV replication appears to play an important role. Compared with HIV-uninfected participants, only participants with an HIV-1 RNA level greater than 500 copies/mL had a significantly increased risk of HF.
For participants who had baseline and recent HIV-1 RNA levels less than 500 copies/mL, there was no significantly increased risk of HF (Table 2). Antiretroviral therapy was associated with a slightly attenuated risk, although the difference between CART-naive and CART-experienced groups did not reach statistical significance. However, these results should be interpreted carefully given the small number of events in the stratified categories. Our findings that hypertension, obesity, alcohol abuse or dependence, and diabetes mellitus were associated with an increased risk of HF are consistent with reports from other established cohort studies of people without HIV infection and offer the possibility of interventions to reduce the risk of HF. In the current study, we were not able to assess the differential risk between controlled and uncontrolled hypertension or diabetes, but this is an attractive topic for further research.

Secondary infection of the myocardium in HIV-infected persons may also lead to myocarditis, myocardial dysfunction, and HF. Presence of cytomegalovirus, acid-fast bacilli, Toxoplasma gondii, Candida species, Histoplasma capsulatum, Cryptococcus neoformans, and Staphylococcus aureus in the myocardium of HIV-infected patients has been reported. A causal association is not clear in all instances, since in some cases, myocarditis is not associated with adjacent myocyte necrosis on histologic examination and evidence of disseminated disease is not present.

Other causes of heart muscle disease in HIV-infected persons include immunologic damage, nutritional deficiencies (eg, selenium, antioxidant vitamins, and carnitine), and antiretroviral therapy. Zidovudine has been associated with a specific dose-dependent skeletal myopathy attributed to mitochondrial toxicity and with cardiac dysfunction that resolves with discontinuation of the drug. However, in a study in HIV-infected children, zidovudine was not associated with worsening of cardiac function. We were unable to analyze the occurrence of HF associated with any specific antiretroviral drugs.

### Table 3. Association Between HIV Infection and Risk of Incident Heart Failure Among Patients Without a CHD or Alcohol Abuse or Dependence Diagnosis Prior to the Incident Heart Failure Event

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infection</td>
<td>1.92 (1.42-2.61)</td>
<td>1.94 (1.36-2.76)</td>
<td>1.96 (1.29-2.98)</td>
</tr>
<tr>
<td>HCV infection</td>
<td>0.99 (0.68-1.43)</td>
<td>0.99 (0.59-1.66)</td>
<td>1.12 (0.63-1.97)</td>
</tr>
<tr>
<td>Age</td>
<td>1.50 (1.29-1.75)</td>
<td>1.71 (1.47-1.99)</td>
<td>1.49 (1.24-1.79)</td>
</tr>
<tr>
<td>African American race</td>
<td>1.55 (1.16-2.06)</td>
<td>1.34 (0.98-1.83)</td>
<td>1.71 (1.18-2.48)</td>
</tr>
<tr>
<td>BMI &gt;30</td>
<td>1.29 (0.94-1.78)</td>
<td>1.91 (1.37-2.68)</td>
<td>1.49 (0.99-2.20)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.86 (0.64-1.17)</td>
<td>1.00 (0.73-1.39)</td>
<td>0.89 (0.61-1.31)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.14 (1.58-2.89)</td>
<td>2.14 (1.52-3.02)</td>
<td>2.51 (1.67-3.79)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.94 (1.45-2.61)</td>
<td>1.96 (1.41-2.71)</td>
<td>1.81 (1.23-2.68)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.41 (1.04-1.90)</td>
<td>1.32 (0.95-1.83)</td>
<td>1.35 (0.92-1.98)</td>
</tr>
<tr>
<td>History of alcohol abuse or dependence diagnosis</td>
<td>1.53 (1.09-2.15)</td>
<td>1.21 (0.49-3.02)</td>
<td>0.67 (0.27-2.79)</td>
</tr>
<tr>
<td>History of cocaine abuse or dependence diagnosis</td>
<td>0.98 (0.65-1.48)</td>
<td>1.21 (0.49-3.02)</td>
<td>0.67 (0.27-2.79)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CHD, coronary heart disease; CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio.

a Patients without a diagnosis of CHD at study entry were excluded from all models.
b Patients without prior CHD; number of events, 207; number of participants, 8406.
c Patients without prior alcohol abuse or dependence; number of events, 167; number of participants, 5689.
d Patients without prior CHD or alcohol abuse or dependence; number of events, 117; number of participants, 5638.

The role of traditional risk factors in the risk of HF needs to be emphasized. Increasing age, African American race, obesity, hypertension, diabetes, and alcohol use are established risk factors and were also significantly associated with a higher risk of HF in our study. Our data tend to suggest that these factors increase the risk of HF independent of their risk on clinically diagnosed CHD, evidenced by the fact that they remained significant even after people with prior CHD were excluded from the study. However, this finding should be interpreted with caution because we could not exclude subclinical CHD. Interventions to minimize the modifiable traditional risk factors, including glycemic and blood pressure control, weight reduction, and abstinence from alcohol, are prudent strategies that should be emphasized. The actual effect of such strategies on risk reduction among HIV-infected persons requires further study.
The strengths of our study include large numbers, participants drawn from validated and well-established cohorts, a national rather than geographically limited sample, and availability of HIV-uninfected controls. Certain limitations need to be understood as well. The diagnosis of HF was based on ICD-9 codes; however, codes for various cardiovascular endpoints have been extensively used in previous publications\(^1,2,4\) and are considered reasonable alternatives to adjudicated clinical outcomes. Moreover, since HF is a chronic condition, our ability to capture outpatient clinical diagnoses in the present study is advantageous; if the initial diagnosis of HF were made at an outside hospital, the diagnosis could be captured in our study via routine follow-up outpatient care within the VA health care system. We did not assess the effect of specific antiretroviral drugs owing to the small number of events for individual drugs, nor did we assess the role of adherence to medication therapy and control of blood pressure or blood glucose levels in the risk of HF. Our study was limited to men and so may not be generalized to women. Other than men being the predominant population, the HIV infection epidemic in veterans is largely similar to that in nonveterans.\(^10\) Since we used administrative data to identify incident HF events, this study was not able to distinguish between HF associated with systolic vs diastolic dysfunction. Finally, while we excluded diagnosed CHD as a preceding event to HF, we did not exclude subclinical atherosclerosis as a cause of HF.

There are major clinical implications of our findings. If HF is a major cardiovascular consequence of HIV infection rather than atherosclerotic heart disease, different approaches to manage such consequences are warranted. Cardiovascular risk factor reduction and antplatelet agents (eg, aspirin) are the mainstay in the management of atherosclerotic heart disease; however, these strategies, plus aggressive blood pressure control and the treatment of the HIV infection, may also be required to prevent development of HF in this population. The exact approach would depend on the mechanism and mediators of this risk; therefore, further studies are needed. Several risk factors identified are modifiable, and intervention studies may be designed to look at the effect of strict blood pressure control, tight glycemic control, and weight loss on the risk of HF. Additional studies are also warranted to fully understand the mechanism of HF in HIV-infected persons, especially to understand the nature of HF, eg, systolic vs diastolic dysfunction.

In conclusion, HIV infection is associated with an increased risk of HF after adjusting for traditional risk factors for HF. This association persisted even after exclusion of patients with a baseline history of CHD, HF, and angina, as well as a CHD event in the follow-up period prior to the diagnosis of HF and a history of alcohol abuse or dependence diagnosis. Ongoing viral replication is associated with a higher risk of HF. Further studies to fully characterize this association and to understand the underlying mechanisms are warranted.

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REFERENCES

patients in the highly active antiretroviral treatment era. AIDS. April 2003;17(suppl
1):S70-S76.

1735.

3. Bozzette SA, Ake CF, Tam HK, Chang SW, Louis TA. Cardiovascular and cere-
brovascular events in patients treated for human immunodeficiency virus infec-


5. Kristoffersen US, Lebech AM, Gerstoft J, et al. Right and left cardiac function in
HIV-infected patients investigated using radionuclide ventriculography and brain

tional study of the incidence of coronary artery disease in patients with HIV in-
fection receiving highly active antiretroviral therapy. Clin Ther. 2003;25(9):
2405-2418.

7. El-Sadr WM, Lundgren JD, Neaton JD, et al; Strategies for Management of An-
tiretroviral Therapy (SMART) Study Group. CD4+ count-guided interruption of

8. Lichtenstein KA, Armon C, Buchacz K, et al; HIV Outpatient Study (HOPS) In-
vestigators. Low CD4+ T cell count is a risk factor for cardiovascular disease


10. Kloner RA, Rezkalla SH. To drink or not to drink? that is the question. Circula-

11. Currie PF, Boon NA. Immunopathogenesis of HIV-related heart muscle disease:

12. Dalakas MC, Illa I, Pezeshkpour GH, Laukaitis JP, Cohen B, Griffin JL. Mitochon-
322(16):1098-1105.

13. Khunnawat C, Mukerji S, Havielke D Jr, Tourma R, Abela GS. Cardiovascular mani-
festations in human immunodeficiency virus–infected patients. Am J Cardiol.

14. McDonald GL, Kaltman JR. Cardiovascular disease in adult and pediatric HIV/AIDS.

dent heart failure and their relationship with obesity: the MESA (Multi-Ethnic Study

tual” cohort using the National VA Health Information System. Med Care. 2006;

17. Butt AA, Fultz SL, Kwoh CK, Kelley D, Skanderson M, Justice AC. Risk of dia-
betes in HIV-infected veterans pre- and post-HAART and the role of HCV coinfection.

18. McGinnis KA, Fultz SL, Skanderson M, Conigliaro J, Bryant K, Justice AC. He-
patocellular carcinoma and non-Hodgkin’s lymphoma: the roles of HIV, hepata-

cal and psychiatric illness and substance abuse in HCV-infected and uninfected


22. Butt AA, McGinnis KA, Skanderson M, Justice AC. Hepatitis C treatment comple-

23. Lee DS, Donovan L, Austin PC, et al. Comparison of coding of heart failure and
comorbidities in administrative and clinical data for use in outcomes research.

24. Petersen LA, Wright S, Normand SL, Daley J. Positive predictive value of the di-
dagnosis of acute myocardial infarction in an administrative database. J Gen Intern

25. Butt AA, Xiaoqiang W, Boudot M, Leaf D, Koller LH, Justice AC. Hepatitis C virus
232.

26. Ives DG, Fitzpatrick AL, Bied DE, et al. Surveillance and ascertainment of cardio-
278-285.

and care services use in human immunodeficiency virus (HIV)-infected and HIV-

28. Grambsch P, Therneau T. Proportional hazards tests and diagnostics based on
.S15.

29. Reinsch N, Neuhaus K, Esser S, et al; German Competence Network for Heart
Failure; German Competence Network for HIV AIDS. Prevalence of cardiac dia-
stolic dysfunction in HIV-infected patients: results of the HIV-HEART study. HIV

30. Hsu PY, Hunt PW, Ho JE, et al. Impact of HIV infection on diastolic function and
left ventricular mass. Circ Heart Fail. 2010;3(1):132-139.

31. Fisher SD, Easley KA, Orav EJ, et al; Pediatric Pulmonary and Cardiovascular Com-
plications of Vertically Transmitted HIV Infection (P2C2 HIV) Study Group. Mild
dilated cardiomyopathy and increased left ventricular mass predict mortal-
439-447.

32. Reilly JM, Cunnion RE, Anderson DW, et al. Frequency of myocarditis, left ven-
tricular dysfunction and ventricular tachycardia in the acquired immune defi-

33. Anderson DW, Virmani R, Reilly JM, et al. Prevalent myocarditits at necropsy in
the acquired immunodeficiency syndrome. J Am Coll Cardiol. 1988;11(4):792-
799.

34. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Levy D. Left ventricular dilata-
tion and the risk of congestive heart failure in people without myocardial infarc-

35. Ingelsson E, Sandstrom J, Arntz J, Zethelius B, Lind L. Insulin resistance and

36. Wu TC, Pizzorno MC, Hayward GS, et al. In situ detection of human cytogena-
tivus immediate-early gene transcripts within cardiac myocytes of patients with

37. Lipshultz SE, Orav EJ, Sanders SP, Hale AR, McIntosh K, Colan SD. Cardiac struc-
ture and function in children with human immunodeficiency virus infection treated