REVIEW ARTICLE

Epidemiology and Pathogenesis of Human Immunodeficiency Virus (HIV) Related Heart Disease: A Review

*M.U. Sani FWACP, **B.N. Okeahialam FWACP
Departments of Medicine, *Aminu Kano Teaching Hospital, Kano, Nigeria and ** Jos University Teaching Hospital, Jos, Nigeria.

ABSTRACT

Background: *There is a clear and growing body of evidence for cardiac dysfunction in a significant portion of patients with HIV disease. An increased number of HIV-infected individuals may present with cardiac complications in the future as more patients with this disease survive longer because of modern therapy. Heart involvement in AIDS may be well characterized cardiac disease occurring coincidentally in AIDS patients, a complication of the disease or its treatment or possibly a direct insult to the heart by the HIV itself.*

Methods: *We reviewed the literature on heart disease in HIV infection and AIDS with particular reference to epidemiology and pathogenetic mechanisms that may play a role in diagnosis, management, and therapy of these complications. The MEDLINE/PUBMED and bibliographic searches for English language studies were used.*

Results: *A variety of potential aetiologies have been postulated in HIV-related heart disease, including myocardial invasion with HIV itself, opportunistic infections, viral infections, autoimmune response to viral infection, drug-related cardiac toxicity, nutritional deficiencies, and prolonged immunosuppression.*

Conclusion: *An increased number of HIV-infected individuals present with cardiac complications as chronic viral infection, co-infections, drug therapy, and immunosuppression. Understanding the nature and course of cardiac illness related to HIV infection may allow appropriate monitoring, early intervention and therapy.*

KEYWORDS: *Epidemiology; Pathogenesis; Heart disease; HIV/AIDS.*

Paper accepted for publication 25th May 2005.

INTRODUCTION

In the early stages of the HIV epidemic cardiac involvement did not feature prominently. Currently there is a clear and growing body of evidence for cardiac dysfunction in a significant portion of patients with HIV disease[1]. An increased number of HIV-infected individuals may present with cardiac complications in the future as more patients with this disease survive longer because of modern therapy. Understanding the nature and course of cardiac illness related to HIV infection will allow appropriate monitoring, early intervention and therapy. It will also provide a baseline to evaluate the effects of new therapeutic regimens such as highly active antiretroviral therapy (HAART) on the cardiovascular system[2,3].

There is a wide range of hypotheses regarding the pathogenesis of HIV associated heart disease. These include myocardial invasion with HIV itself, opportunistic infections, viral infections, autoimmune response to viral infection, drug-related cardiac toxicity, nutritional deficiencies, and prolonged immunosuppression[4].

The actual pathogenesis of cardiac injury in HIV infection is not clear. It is however generally agreed that several factors come into play either singly or in combination to produce cardiac pathology.

Table I. Medications used in HIV infection and their toxic effects on the heart*

Medications	*Treatment*	*Cardiovascular effect*
Amphotericin B	Antifungal	Dilated cardiomyopathy, Hypertension and bradycardia
Doxorubicin	Kaposi sarcoma	Cardiomyopathy
Epoetin alfa	Anaemia	Hypertension
Foscarnet Sodium	CMV	Cardiomyopathy
Ganciclovir	CMV	Ventricular tachycardia
HAART	Antiretroviral	Peripheral vascular disease coronary artery disease
Interferon alfa	Antineoplastic Antiviral Immunomodulator	Arrhythmia, myocardial infarction or ischemia cardiomyopathy, AV block sudden death and CCF
Pentamidine	*Pneumocystis carinii*	QT prolongation Torsades de pointes
Pyrimethamine	Toxoplasmosis	QT prolongation
Trimethoprim-Sulfamethoxazole	*Pneumocystis carinii*	QT prolongation Torsades de pointes
Zidovudine	Antiretroviral	Myocarditis and dilated Cardiomyopathy

*HIV indicates human immunodeficiency virus; CMV, cytomegalovirus; HAART, highly active antiretroviral therapy; CCF, congestive cardiac failure

Correspondence to: **Dr M.U. Sani**

Epidemiology Of HIV Related Heart Disease

The exact prevalence of cardiac involvement in AIDS patients is unknown[5]. It is however known that the frequency of involvement depends on the population studied, the definition of cardiac abnormality and the method of patient assessment. Although small autopsy series from the early 1980s noted some cardiac abnormality in 25% to 73% of cases[6-8], it appeared that the cardiac findings were of little clinical significance. Few if any of the patients in these series had symptoms or a cause of death attributable to cardiac pathology. More recent estimates from autopsy series suggest that significant cardiovascular pathology occurs in over 30% of patients[9]. More importantly, clinically significant cardiac disease occurs in approximately 2.1% to 7.5% of persons infected with HIV[10-12].

When the heart is examined echocardiographically or electrocardiographically (ECG), the prevalence of cardiac involvement is higher than would be expected from clinical symptomatology. The prevalence is also affected by the spectrum of HIV disease.

Levy *et al*[5] described cardiac abnormalities in 53 % of HIV infected patients,36% of whom were asymptomatic. In the same study they found that abnormalities were more common in those with opportunistic infections than those without (62% vs 73%). In Africa recent studies have shown that HIV may have a cardiac tropism. Longo-Mbenza *et al*[13] in Kinshasa reported cardiac lesions in 55% of 157 consecutive HIV infected patients during a 7 year follow-up period who at entry had no cardiac disease or other AIDS defining illness. Malu *et al*[14] reported that 50% of their patients had cardiac lesions in Zaire.

In Nigeria, Okeahialam *et al* [15] working in Jos described cardiac symptoms in 58 % of AIDS patients studied and pericardial involvement in 47% of them using an echocardiograph.

ECG abnormalities were described by Levy *et al*[5] in 28% of 18 asymptomatic HIV infected patients and 53% of 32 patients with clinical AIDS. In Chad, Mouanodji *et al*[16] described ECG abnormalities in 86% of 55 patients with clinical AIDS, 61% of whom had cardiac symptoms. Herst *et al*[17] described abnormal ECG in 55% of 21 patients with Kaposi's sarcoma (KS) none of whom had cardiac symptoms.

Direct HIV Myocardial Invasion

Although it is clear that HIV can affect myocardial interstitial cells, the evidence that the virus can enter cardiac myocytes which do not possess CD_4 receptors is less clear[18]. HIV was isolated in culture from an endomyocardial biopsy specimen from a patient with AIDS and dilated cardiomyopathy[19]. Using immunocytochemical tests, the HIV-1 antigen has been found in endothelial cells from an endomyocardial biopsy of a patient with left ventricular hypokinesia [20]. Additionally the HIV nucleic acid sequences have been reported in the myocardium of HIV infected patients using in-situ hybridization[21]. In that study the distribution of the hybridization assay signal in heart tissue was sparse and did not correlate with any histopathologic or clinical evidence of heart disease. Rodriguez *et al* [22] isolated individual myocardial cells from right ventricular biopsy by micro dissection. Using multiplex nested polymerase chain reaction (PCR) they identified HIV sequences in 2 of 5 patients with cardiac symptoms and 6 of 10 patients without cardiac symptoms who had normal ventricular function. Thus, the presence of the organism did not correlate with cardiac abnormalities of structure or function. Furthermore, HIV sequences might have been contaminants from other cells or from blood since PCR technique is very sensitive[19] and immunohistochemical studies have shown no evidence of group 120 or p24 antigen expression on the heart[23]. It has however been recently shown through in vitro studies that newly developed human foetal cardiac myocyte cell line could ingest HIV-1 through a specific F_c receptor despite absence of CD_4 receptors on the myocytes[24].

Opportunistic Infections

Since HIV infection results in profound suppression of T Cell macrophage mediated immunity and since there are significant abnormalities in B cell lymphocytic function leading to abnormalities of humoral immunity, patients with HIV disease frequently face many life threatening infections by bacterial, fungal, parasitic and viral organisms.

Organisms implicated in the pathogenesis of pericarditis are *staphylococcus aureus, streptococcus pneumoniae, norcardia asteroides, listeria monocytogenes, rhodococcus equi, chlamydia trachomatis, mycobacterium tuberculosis, mycobacterium avium-intracellulare,* and *mycobacterium kansasi*. Others are *Cryptococcus neoformans, histoplasma capsulatum, toxoplasma gondii, cytomegalovirus* and *Herpes simplex*[25,26].

Among patients with myocarditis, opportunistic bacterial, fungal, and protozoan pathogens can be

identified in 10 to 15 percent of cases. In one autopsy series, 12 percent of 182 patients had cardiac toxoplasmosis[27].

Cytomegalovirus is another common opportunistic infection in patients with late stage AIDS that can cause myocarditis in selected patients[28]. Coxsackie virus infection is another possible aetiology[29].

Role Of Cytokines

There is increasing evidence that immune cells especially T lymphocytes are activated to produce cytokines in HIV disease. Patients with HIV disease produce excessive levels of cytokines mainly tumour necrosis factor (TNF), interferon alpha (IF alpha), interleukin-1 and interleukin-2. These cytokines may cause decreased myocardial function[30]. Increased levels of TNF-alpha and inducible nitric oxide synthase (iNos) have been reported in patients with HIV associated dilated cardiomyopathy with iNos staining intensity correlating with mortality and degree of immunosuppression[31]. It is not clear whether these cytokines act locally in the adjacent myocardium or whether they are present in sufficient quantity in the serum to cause myocardial depression.

HIV may also inflict damage on myocytes by means of a mechanism of "innocent bystander destruction" proposed by Ho *et al*[32] for neurological cell damage in AIDS associated sub acute encephalitis. According to this hypothesis, the myocytes are damaged by the toxic enzymes and cytokines released through HIV replication in the interstitium and it may be particularly relevant to the myocardium, since increased numbers of infected interstitial cells have been found in HIV positive subjects with active myocarditis[22].

The Autonomic Nervous System

Patients with AIDS are subject to long term physiologic stress due to tragic implications of their disease; the pathway being mediated through prolonged and excessive secretion of catecholamines. This may in turn lead to intermittent microvascular spasm and focal or widespread ischaemia[33] resulting in cardiac damage as seen in some cases of phaeochromocytoma[34]. Autonomic imbalance may also be related to HIV induced neural pathway damage[35] or may be a result of direct beta receptor stimulation by group 120 protein[36]. These theories are yet to be explored, but they do offer a possible explanation for the presence of non-inflammatory myocardial necrosis associated with AIDS.

Nutritional Deficiencies

Nutritional deficiencies are common in HIV infection as a result of reduced intake and malabsorption[37] . In particular, recent reports have described abnormally low levels of serum selenium in paediatric AIDS patients[38] and in autopsy tissue samples of adult myocardium [39]. Selenium deficiency is responsible for Keshan disease; a form of dilated cardiomyopathy in China[40]. Zazzo *et al* reported non obstructive cardiomyopathy associated with selenium deficiency in patients with advanced HIV disease. The patients improved with selenium repletion[41].

Other specific nutritional deficiencies include B group vitamins, folates and zinc[42,43]. Some of these may be mediated by increased levels of tumour necrosis factor[44]. These deficiencies could worsen immune function or contribute to cardiac dysfunction[42,43].

Cachexia is common in HIV disease, and wall motion abnormalities and less commonly congestive heart failure have been reported in non HIV infected patients with severe weight loss, anorexia nervosa and starvation[45].

Drugs and Toxins

The advent of potent antiretroviral drugs in recent years has had an impressive impact on mortality and disease progression in HIV-infected patients, so that issues related to long-term effects of drugs are of growing importance[46]. A metabolic syndrome characterised by dyslipidemia, lipodystrophy/ lipoatrophy and insulin resistance is increasingly described as an adverse effect of highly active antiretroviral therapy (HAART), in particular when protease inhibitors are used[47]. This metabolic syndrome may be associated with an increase in peripheral artery and coronary artery diseases[48].

Patients with HIV are exposed to many medications to treat conditions related to HIV diseases such as cancer and opportunistic infections. Some of these medications have cardiovascular toxicities. QT interval prolongation and/or torsade de pointes, a life-threatening ventricular arrhythmia have been reported in patients treated with pyrimethamine[49], pentamidine[50], combination of trimethoprim and sulphamethoxazole[51] and clarithromycin[52]. Cohen and co-workers[53] described ventricular tachycardia following intravenous infusion of Ganciclovir for CMV. Interferon alpha, an antineoplastic, antiviral and immunomodulator has been reported to have a variety of reversible cardiotoxic effects[54] .These

include arrhythmias, myocardial infarction or ischaemia, sudden death, AV block, cardiomyopathy and congestive cardiac failure.

Anthracyclines like doxorubicin are potent cytotoxic antibiotics that have been widely used for the treatment of HIV-related neoplasms. Their cardiotoxicity is well known, ranging from benign and reversible arrhythmias to progressive severe cardiomyopathy[55].

Amphotericin B used for disseminated fungal infection has been reported to cause reversible dilated cardiomyopathy[56], bradycardia[57] and hypertension[58]. Reversible cardiomyopathy has been described in HIV patients treated with forscarnet sodium for cytomegalovirus (CMV) oesophagitis[59]. Cardiac dysfunction has been found in adults and children treated with Zidovudine, a nucleoside analogue reverse transcriptase inhibitor[60]. Diffuse destruction of cardiac mitochondrial ultrastructures and inhibition of mitochondrial DNA replication may be responsible for Zidovudine induced cardiomyopathy[61].

Among HIV-infected patients with cardiac abnormalities, the incidence of alcohol, cocaine and injection drug use is high. An abnormal diastolic function has been demonstrated in patients with substance abuse at various stages of HIV infection and in a control group who were HIV negative[62] (Table I).

Immunosuppression/Autoimmunity

Some studies have indicated immunosuppression predisposing to myocarditis. The study by Himelman and colleagues[63] in which T4 helper lymphocytes were used as markers of immunosuppression failed to show any quantitative difference in T4 cells between HIV patients with and without cardiomyopathy/myocarditis.

It has been hypothesized that altered T helper cell function induces myocardial inflammation by uncontrolled hypergammaglobulinaemia[64]. The HIV gene may provoke cell surface cardiac muscle protein resulting in induction of circulating cardiac auto antibodies which can trigger a progressively destructive autoimmune reaction[65]. Circulating auto antibodies have been identified by means of indirect immunoflourescence in four of six AIDS patients with cardiomyopathy but in none of HIV positive patients without cardiomyopathy[66].

In addition high levels of autoantibodies against myosin and cardiac mitochondrial adenosine nucleotide translator have been found in association with MHC Class 1 antigen expression in a small group of HIV positive patients with active myocarditis[67].

Types of Heart Disease in HIV and AIDS

Through one or a combination of above pathogenic mechanisms a wide range of cardiovascular diseases have been described in HIV and AIDS[68]. Pericardial effusion is one of the common types of cardiac involvement in HIV patients, and its mechanism is related to infections or neoplasms[69]. Myocarditis in HIV infection may be caused by the virus itself, either directly or indirectly via autoimmune processes, or by one of many opportunistic organisms. In more than 80% of these patients no specific aetiologic factor was found for the myocarditis[70]. Cardiac failure due to a dilated cardiomyopathy (DCM) was first described in three AIDS patients in 1986[71]. Since then AIDS is increasingly recognized as an important aetiologic factor in this disease. DCM has emerged as the most clinically significant cardiac complication of HIV infection in the western world[72].

Endocardial involvement has been described in HIV infection and AIDS. Both non bacterial thrombotic (marantic)[73] and bacterial endocarditis[74] from different opportunistic organisms have been reported.

Coronary artery disease (CAD) has been reported in a patient with HIV infection[75]. The association of HAART regimens that include protease inhibitors (PIs) with atherosclerosis and atherothrombosis from dyslipoproteinaemia has raised concerns about the possibility of an increased risk of CAD in patients with HIV infection treated with this regimen[76].

Other heart diseases that have been documented in HIV infection are pulmonary hypertension[77], cardiac lymphomas[78] and cardiac Kaposi sarcoma[79].

CONCLUSION

An increased number of HIV-infected individuals present with cardiac complications as chronic viral infection, co-infections, drug therapy, and immunosuppression. Understanding the nature and course of cardiac illness related to HIV infection may allow appropriate monitoring, early intervention and therapy, and will provide a baseline to evaluate the effects of new therapeutic regimens such as highly active antiretroviral therapy on the cardiovascular system. While epidemiological studies have suggested an increased risk for coronary artery disease in HIV infected persons, only long term follow-up could confirm this. Despite these uncertainties, it seems reasonable to identify and

manage cardiovascular risk factors in HIV infected persons.

REFERENCES

1. Jacob AJ, Boon VA. The role of human immunodeficiency virus in heart disease. In: Banatvala JE(ed). Viral Infections of the heart. London: Edward Arnold,1993: 176-195.
2. Fisher SD, Lipshultz SE. Epidemiology of cardiovascular involvement in HIV disease and AIDS. Ann N Y Acad Sci 2001; 946:13-22.
3. Barbarinia G, Barbaro G. Incidence of the involvement of the cardiovascular system in HIV infection. AIDS 2003; 17 (Suppl 1): S46-50.
4. Barbaro G, Lipshultz SE. Pathogenesis of HIV-associated cardiomyopathy. Ann N Y Acad Sci 2001; 946:57-81.
5. Levy WS, Simon GL, Rios J C, et al. Prevalence of Cardiac abnormalities in HIV infection. Am J Cardiol 1989; 63: 86-89.
6. Hui AN, Koss MN, Meyer PR. Necropsy findings in acquired immunodeficiency syndrome. Hum Pathol 1984; 15(7):670-676.
7. Fink L, Reichek N, St. John Sutton MG. Cardiac abnormalities in acquired immune deficiency syndrome. Am J Cardiol 1984; 54:1161-1163.
8. Welch K, Finkbeiner W, Alper CE, *et al.* Autopsy findings in the acquired immune deficiency syndrome. JAMA 1984; 252:1152-1159.
9. Altieri PI, Climent C, Lazala G, *et al.* Opportunistic invasion of the heart in Hispanic patients with acquired immunodeficiency syndrome. Am J Trop Med Hyg 1994; 51:56-59.
10. De Castro S, d'Amati G, Gallo P, *et al.* Frequency of development of acute global left ventricular dysfunction in human immunodeficiency virus infection. J Am Coll Cardiol 1994; 24:1018-1024.
11. Herskowitz A, Vlahov D, Willoughby S, *et al.* Prevalence and incidence of left ventricular dysfunction in patients with human immunodeficiency virus infection. Am J Cardiol 1993; 71:955-958.
12. Anderson DW, Virmani R. Emerging patterns of heart disease in human immunodeficiency virus infection. Hum Pathol 1990; 21:253-259.
13. Longo-Mbenza B, Seghers KV, Phuati M, *et al.* Heart involvement and HIV infection in African Patients; Determinants of Survival. Int J Cardiol 1998; 64: 63-73.
14. Malu K, Longo-Mbenza B, Lurhuma Z, Odio W. Pericarditis and AIDS. Arch Mal Coeur Vaiss 1988; 81: 207-211.
15. Okeahialam BN, Anjorin FI. Echocardiographic study of the heart in AIDS. The Jos Experience. Trop Card 2000; 26:3-6.
16. Mouanodji M, Mbaigonro D, Brendan P. Clinical Outline of AIDs patients with Cardiac manifestations in Africa. Int Conf AIDS 1994; 10: 266 (abstract No PB 0495).
17. Herst JA, Shepherd FA, Liu P, *et al.* Prospective assessment of Cardiac function in Patients with Kaposis sarcoma and AIDS. Clin Inv Med 1991; 14: 21-27.
18. Wu AY, Forouha, Cartun RW, *et al.* Identification of HIV in the heart of a patient with AIDS. Mod Path 1990;3:625-630.
19. Calabarese L, Proffitt M, Yen-Liberman B, *et al.* Congestive Cardiomyopthy and illness related to the acquired immunodeficiency Syndrome (AIDS) associated with isolation of retrovirus from myocardium. Ann Intern Med 1989; 107: 691-692.
20. Cenacchi G, Re MC, Furlini G, *et al.* Human immunodeficiency virus type I antigen detection in endomyocardial biopsy: an immunomorphological study. Microbiologica 1990; 13: 145-149.
21. Grody WW, Cheng L, Lewis W. Infection of the heart by the HIV. Am J Cardiol 1990; 66: 203-206.
22. Rodriguez ER, Nasi MS, Hsia J, *et al.* Cardiac myocytes and dendritic cells harbour human immunodeficiency virus in infected patients with and without cardiac dysfunction: detection by multiplex, nested, PCR in individually micro-dissected cells from right ventricular biopsy tissue. Am J Cardiol 1991; 68: 1511-1520.
23. Jacob AJ, Rebus S, Bird AG, *et al.* Can HIV infect the heart? (abstract). Eur Heart J 1992; 13:370.
24. Herskowitz A, Willoughby S, Wu TC, *et al.* Immunopathogenesis of HIV 1 associated cardiomyopathy. Clin Immunol Immunopathol 1993; 68:234-241.
25. Decker CF, Tuazon CU. *Staphylococcus aureus* pericarditis in HIV infected patients. Chest 1994; 105:615-616.
26. Freedberg RS, Gindea AJ, Dieterich DT, Green JB. Herpes simplex type 2 pericarditis and bilateral facial palsy in a patient with AIDS. N Y state J Med 1987; 87:304-306.
27. Horman D, Drici MD, Gibelin P, *et al.* Prevalence of toxoplasma myocarditis in patients with the acquired immunodeficiency syndrome. Br Heart J 1993; 70:376-381
28. Niedt GW, Schinella RA. Acquired immunodeficiency syndrome. Clinicopathologic study of 56 autopsies. Arch Pathol Lab Med 1985; 109:727-734.
29. Dittrich, H, Chow, L, Denaro, F, Spector, S. Human immunodeficiency virus, coxsackievirus, and cardiomyopathy (letter). Ann Intern Med 1988;108:308.
30. Sonnenblick M, Rosenmann D, Rosin A. Reversible Cardiomyopathy induced by interferon. BMJ 1990; 300: 1174-1175.
31. Barbaro G, Dilorenzo G, Soldini M, *et al.* Intensity of myocardial expression of inducible nitric oxide synthase and how it influences the clinical course of HIV associated cardiomyopatly. GISCA. Circ 1999; 100 : 933-939.
32. Ho DD, Pomerantz RT, Kaplan JC. Pathogenesis of infection with HIV. N Engl J Med 1987;317:278-286.
33. Factor SM, Sonnenblick EH. The pathogenesis of clinical and experimental congestive cardiomyopathies and recent concepts. Prog Cardiovasc Dis 1985;27:395-420.
34. Sardesai SH, Mourant AJ, Siva thandon Y, et al Phaechromocytoma and catecholamine induced cardiomyopathy presenting as heart failure. Br Heart J 1990; 63: 234-237.
35. Freeman R, Roberts MS. Friedman LS, Broadbridge C. Autonomic function and HIV infection. Neurology 1990;40:575-580.
36. Glulio L, Petrucci T, Patrizio M, Bernado A. HIV envelope glycoprotein (gp 120) interacts with astroglial beta adrenergic receptors. Int Conf AIDS (Florence) 1991; abstract MA 1037.
37. Kotler DP. Nutritional effects and support in the patient with AIDS. J Nutrition 1992; 122:723-727
38. Jacob AJ, Fell GS, Boon NA. Is HIV cardiomyopathy related to deficiency of selenium? Br Heart J 1992; 68:137-142.
39. Dworkin BM, Antonecchia PP, Smith F, *et al.* Reduced cardiac selenium content in AIDS. J Parentre Enter Nutr 1989; 13:644-647.
40. Keshan Disease Research Group- observations of the effect of sodium selenite on prevention of Keshan disease. Chin Med J 1979;92:471-476.

41. Zazzo JF, Chalas J, Lafont A, *et al.* Is non obstructive cardiomyopathy in AIDS a selenium deficiency related disease? J Parenter Enter Nutr 1988; 12: 337-338.
42. Beach RS, Cabrejos C, Montero Atunza E, *et al.* Effect of zinc normalization on immunological function in early HIV 1 infection. Int Conf AIDS (Florence) 1991; abstract MC 3128.
43. Baum MK, Mantero-Atunza EM, Shor Posner G, et al. Association of Vit B6 status with parameters of immune function in early HIV 1 infection. J Acq Immune Def Syndr 1991;4:1122-1132.
44. Beutler B. The presence of cachectin/TNF in human disease states. Am J Med 1988; 85: 287-288.
45. Schocken DD, Holloway TD, Powers PS. Weight loss and the heart: effects of anorexia nervosa and starvation. Arch Intern Med 1989; 149:877- 881.
46. Fantoni M, Autore C, Del Borgo C. Drugs and cardiotoxicity in HIV and AIDS. Ann N Y Acad Sci 2001;946:179-99.
47. Barbaro G. HIV infection, highly active antiretroviral therapy and the cardiovascular system. Cardiovasc Res 2003; 60(1):87-95.
48. Barbaro G, Fisher SD, Lipshultz SE. Pathogenesis of HIV-associated cardiovascular complications. Lancet Infect Dis 2001;1(2):115-24.
49. Von Seildlein L, Jaffar S, Greenwood B. Prolongation of QTc interval in African children treated for falciparum malaria. Am J Trop Med Hyg 1997; 56:494-497.
50. Stein KN, Haronian H, Mensah GA, *et al.* ventricular tachycardia and torsades de pointes complicating Pentamidine theraphy for Pneumocystis carinii pneumonia in AIDS. Am J Cardiol 1990; 66:888-889.
51. Lopez JA, Harold JG, Rosenthal MC, *et al.* QT prolongation and torsades de pointes after administration of trimethoprim-sulfamethoxazole. Am J Cardiol 1987; 59:376-377.
52. Vallejo Camazon N, Rodriguez Pardo D, Sanchez Hidalgo A, Tornos Mas MP, Ribera E, Soler Soler J. Ventricular tachycardia and long QT associated with clarithromycin administration in a patient with HIV infection. Rev Esp Cardiol 2002; 55(8):878-81.
53. Cohen AJ, Weiser B, Afzal Q, Fuhrer J. Ventricular tachycardia in two patients with AIDS receiving ganciclovir (DHPGS). AIDS 1990; 4: 807-809.
54. Sonnenblick M, Rosin A. Cardiotoxicity of interferon: a review of 44 cases. Chest 1991; 99: 557-561.
55. Bristow MR, Mason JW, Billingham ME, Daniels JR. Doxorubicin cardiomyopathy: evaluation by phonocardiography, endomyolardial biopsy and cardiac catheterization. Ann Inter Med 1978; 88:168-175.
56. Arsura EL, Ismail Y, Freeman S, *et al.* Amphotericin B induced cardiomyopathy. Am J Med 1994; 97:560-562.
57. Levy M, Domaratzki J, Koren G. Amphotericin induced heart rate decrease in children. Clin Pediatr (Phila) 1995; 34:358-364.
58. Le Y, Rana KZ, Dudley MN. Amphotericin B associated hypertension. Ann Pharmacother 1996; 30:765-767.
59. Brown DL, Sather S, Cheitlin MD. Reversible cardiac dysfunction associated with foscarnet therapy for CMV esophagitis in an AIDS patients. Am Heart J 1993; 125:1439-1441.
60. Herskowitz A, Willoughby SB, Baughman KL, *et al.* Cardiomyopathy associated with antiretroviral therapy in patients with human immunodeficiency virus infection: a report of six case. Ann Intern Med 1992; 116:311-313.
61. Lewis W, Simpson JF, Meyer RR. Cardiac mitochondrial DNA polymerase-gamma is inhibited competitively and non-competitively by phosphorylated zidovudine. Circ Res 1994; 74: 344-348.
62. Cheitlin MD, Schiller NB, Kee L, *et al.* Longitudinal echocardiographic AIDS project: effect of substance abuse on left ventricular function. Int Conf AIDS (San Francisco) 1990; Abstact No. FB 529
63. Himelman RB, Churg WS, Chernoff DN, *et al.* Cardiac manifestation of HIV infection, 2D echocardiographic study. J Am Coll Cardiol 1989; 13:1030-1036.
64. Acierno LJ. Cardiac Complications in AIDS: a review. JAm Coll Cardiol 1989; 13: 1144-1154.
65. Herskowitz A, Neuman DA, Ansari AA. Concepts of autoimmunity applied to idiopathic dilated cardiomyopathy. J Am Coll Cardiol 1993; 22:1385-88.
66. Herskowitz A, Willoughby SB, Vlahov K, *et al.* Dilated heart muscle disease associated with HIV infection. Eur Heart J 1995; 16:50-55.
67. Herskowitz A, Ansari AA, Neuman DA, *et al.* Cardiomyopathy in AIDS: evidence of autoimmunity. J Am Coll Cardiol 1993;22(5):1385-8
68. Barbarinia G, Barbaro G. Incidence of the involvement of the cardiovascular system in HIV infection. AIDS 2003; 17 (Suppl 1): S46-50.
69. Pairaj R, Nattawul W, Larry J, *et al.* Cardiac manifestation of AIDS. Arch Inter Med 2000; 160: 602-608.
70. Kaul S, Fishbein MC, Siegel RJ, *et al.* Cardiac manifestations of AIDS. Am Heart J 1991; 122:535-544.
71. Cohen IS, Anderson DW, Virmani R, *et al.* Congestive cardiomyopathy in association with AIDS. N Engl J Med 1986; 315: 628-630.
72. Decastro S, D'Ameti G, Gallo P, *et al.* Frequency of development of acute global Left ventricular dysfunction in HIV infection. J Am Coll Cardiol 1994; 24:1018-1024.
73. Commarosano C, Lewis W. Cardiac Lesions in AIDS. (Spannish). J Am Coll Cardiol 1985; 5: 703-706.
74. Lewis W, Grody WN. AIDS and the heart: review and consideration of pathologic mechanisms. Cardiovasc Pathol 1992;1:53-64.
75. Tabib A, Greenland T, Mercier I, et al. coronary lessons in young HIV positive subject, at necropsy (letter). Lancet 1992; 340:730.
76. Barbaro G, Di Lorenzo G, Cirelli A, et *al* An open-label, prospective, observational study of the incidence of coronary artery disease in patients with HIV infection receiving highly active antiretroviral therapy. Clin Ther 2003;26(9):2405-18. Erratum in: Clin Ther 2004;26(1):175.
77. Kim KK, Facto SM. Membranoproliferative glomerulonephritis and plexogenic pulmonary arteriopathy in homosexual men with AIDS. Hum Pathol 1987; 18:1293-1296.
78. Biggar RJ, Rabkin CS. The epidemiology of AIDS related lymphomas. Curr Opin Oncol 1992; 4:883-893.
79. Moskowitz L, Hensley GT, Chan JC, et al. Immediate causes of death in AIDS. Arch Pathol Lab Med 1985;