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section 16 Cardiovascular disorders 3534 16.9.3 Cardiac disease in
HIV infection Peter F. Currie ESSENTIALS Symptomatic heart disease can affect up to 10% of HIV-positive pa- tients and cause death in around 2%. Cardiovascular screening and risk factor management is recommended. In resource-poor countries where access to antiretroviral drugs is limited the typical manifestations are (1) HIV heart muscle disease— this occurs in the late stages of HIV infection, with dilated cardiomy- opathy having a dismal prognosis, the median survival after diagnosis being about 100 days; standard therapy for heart failure should be considered; and (2) pericardial effusion—a common finding, but most are symptomless; significant effusions are often due to myco- bacterial infection or malignant infiltration, particularly with non- Hodgkin's lymphoma. In the developed world, premature coronary artery disease is more common in patients with HIV than in controls. There is a two- to threefold increase in the incidence of acute coronary events in HIV patients treated with highly active antiretroviral therapy, which is thought to be related to HIV lipodystrophy, an ill-defined syndrome that resembles the non-HIV metabolic syndrome and is found in up to 35% of patients after 12 months of protease inhibitor therapy. Isolated pulmonary hypertension is a rare, noninfectious com plication of HIV infection and has a grave prognosis (50% survival at 1 year). Highly active antiretroviral therapy and specific pulmonary hypertension therapies may provide symptomatic relief. There are many important interactions between commonly used cardiac medications and components of highly active antiretroviral therapy. These should be carefully considered when managing car- diovascular conditions in this population. Introduction Cardiovascular manifestations of HIV infection are well recognized and have been reported in up to 40% of autopsies and about 25% of echocardiographic studies performed on patients with AIDS. While most of these lesions are minor, symptomatic heart disease can affect up to 10% of HIV-positive patients and cause death in around 2%. Heart muscle disease was previously the dominant cardiac com- plication of HIV infection in the developed world

until the advent of highly active antiretroviral therapy (HAART). This has signifi- cantly altered the course of HIV infection and most likely reduced the incidence of heart muscle disease and other forms of heart dis- ease in AIDS. However, HAART-induced dyslipidaemia has become an important factor for the development of premature coronary ar- tery disease, which is becoming increasingly common. Despite sig- nificant progress in providing HAART to increasing numbers of patients in the developing world, HIV heart muscle disease, pericar- dial effusion, and pulmonary hypertension continue to predominate in resource-poor countries where access to antiretroviral drugs is limited. The common cardiovascular manifestations of HIV infection are listed in Table 16.9.3.1. HIV/AIDS and the pericardium Pericardial effusion and pericarditis were found frequently in early HIV autopsy studies and still remain a significant problem in Africa. Small effusions are common, but most are symptomless. Cardiac tamponade is rare, but the finding of unexplained breath- lessness, raised jugular venous pressure, or radiographic cardio- megaly should prompt early echocardiographic assessment (see Chapter 16.8). In Africa up to 72% of patients with serosanguinous effusions have been found to be HIV-positive, and Mycobacterium tubercu- losis or M. avium-intracellulare pericarditis is common. Appropriate antituberculous and antiviral therapies may be helpful, but it is not clear if corticosteroids are beneficial in this situation and they are generally avoided. Herpes simplex virus, cytomegalovirus, and other unusual organisms may clinically be implicated, but clinically significant pericardial effusions are often due to malignant infiltra- tion, particularly with non-Hodgkin’s lymphoma. Pericardiocentesis and pericardiectomy can be used to treat tam- ponade in HIV infection, but surgical intervention may not be ap- propriate in patients with very advanced disease. Clearly, however, culture of pericardial biopsy or fluid from symptomatic effusions may be useful in identifying treatable opportunistic infections or malignancy.
Table 16.9.3.1 Cardiovascular manifestations of HIV/AIDS Pericardial effusion Idiopathic Infectious (viral, bacterial—especially tuberculous, and fungal) Neoplastic (Kaposi’s sarcoma and non-Hodgkin’s lymphoma) Heart muscle disease Myocarditis (idiopathic/lymphocytic, specific infections, toxins) Dilated cardiomyopathy Left ventricular dysfunction Isolated right ventricular dysfunction Endocarditis Marantic (nonbacterial thrombotic endocarditis) Infective Pulmonary hypertension Primary Secondary (recurrent bronchopulmonary infections, thromboembolism) Premature atherosclerosis and coronary artery disease Stroke Adverse drug effects Hyperlipidaemia Induction of arrhythmia Autonomic dysfunction Sudden death

16.9.3 Cardiac disease in HIV infection 3535 Cardiac tumours in HIV/AIDS In AIDS patients, Kaposi’s sarcoma is a disseminated visceral dis- ease with cardiac involvement in up to 25% of cases. Isolated cardiac Kaposi’s sarcoma is rare. The tumour often invades the subpericardial fat around coronary arteries and may infiltrate the pericardium or myocardium. However, despite this, Kaposi’s sarcoma is not usually associated with cardiac symptoms and significant effusion is rare. The prevalence of cardiac Kaposi’s sarcoma in HIV/AIDS appears to be falling. Primary cardiac lymphoma is extremely rare in HIV-negative individuals, although disseminated lymphoma may involve the myocardium more frequently. Both patterns of malignant cardiac involvement occur in AIDS patients, and non-Hodgkin’s lymphoma in particular, may involve the pericardium or myocardium. In con- trast to Kaposi’s sarcoma, cardiac lymphoma is commonly associ- ated with tamponade, symptomatic heart failure, and conduction abnormalities. This diagnosis should therefore be considered in AIDS patients with rapidly progressive cardiovascular symptoms, unexpected arrhythmias, or heart block. Endocardial disease in HIV/AIDS Marantic or nonbacterial thrombotic endocarditis was a frequent finding in early AIDS post-mortem series. Noninfectious systemic thromboembolism was a common sequel and hence the condition is associated with

significant morbidity and mortality. It is now rarely described as a complication of AIDS. Although AIDS patients are susceptible to bacterial infections, in- fective endocarditis rarely occurs in HIV infection outwith the set- ting of injection drug use (see Chapter 16.9.2). Asymptomatic HIV infection per se appears to have little effect on the susceptibility to, or the mortality from, the condition, although bacterial endocar- ditis runs a more fulminant course in the late stages of AIDS. In par- ticular, a CD4 count of less than 200 cells/μl is associated with a poor prognosis in these circumstances. As with infective endocarditis in patients who are HIV-negative, in intravenous drug users the tri- cuspid valve is most commonly involved and Staphylococcus aureus or Streptococcus viridans are the most frequently isolated organisms. Aspergillus fumigatus, Pseudallescheria boydii, and other forms of bacterial and fungal endocarditis occur in end-stage AIDS. Just as for patients without AIDS, adequate bacteriological in- vestigations are required when endocarditis is suspected in HIV- positive individuals, but initial ‘best guess’ antimicrobial treatment (see Chapter 16.9.2) may have to be widened, particularly if fungal endocarditis is suspected. Valvular heart surgery has been described in HIV-positive intravenous drug users with endocarditis, but continued drug use often results in a poor prognosis, as in the non- HIV/AIDS population. Heart muscle disease HIV heart muscle disease occurs in the late stages of HIV infection and is associated with low CD4 counts. Before HAART, symptomatic congestive cardiac failure was found in around 5% of HIV patients. However, the signs and symptoms of heart failure were frequently mistakenly attributed to anaemia or bronchopulmonary infection. Left ventricular systolic dysfunction—either isolated or in the form of a dilated cardiomyopathy—could be found echocardiographically in 10–15% of patients with AIDS previously and currently in up to 3% of patients treated with HAART (Fig. 16.9.3.1). The cause or causes of HIV heart muscle disease remain un- known, but are almost certainly complex. It is likely that an auto- immune lymphocytic myocarditis plays a key pathogenic role, in line with current thinking on the pathogenesis of idiopathic dilated cardiomyopathy in HIV-negative patients. Before HAART, some form of myocarditis was found by biopsy or at autopsy in up to 40% of patients with AIDS, and rarely specific organisms were identified (e.g. Toxoplasma gondii or cytomegalovirus), usually in the setting of disseminated infection. Some in situ hybridization studies have suggested that HIV-1 may be present in the myocardium of patients with HIV heart muscle disease, although clear evidence for a pri- mary HIV myocarditis is still lacking. It is possible that the myo- carditis is secondary to an autoimmune reaction mediated through cytokines or circulating cardiac autoantibodies, but other potential cofactors include specific micronutrient deficiencies (especially selenium) or the cardiotoxic side effects of antiretroviral agents. An acute, lymphocytic myocarditis with intractable ventricular arrythmia has also recently been described as part of the immune reconstitution inflammatory syndrome. HIV-related dilated cardiomyopathy has a dismal prognosis in the setting of advanced disease, with median survival after diag- nosis being about 100 days (Fig. 16.9.3.2). Conventional antiheart-failure treatment should be used, but vasodilating agents such as angiotensin-converting enzyme (ACE) inhibitors are often poorly tolerated by end-stage AIDS patients and β-blockers may also pro- duce unacceptable side effects. Diuretics, digoxin, and aldosterone antagonists may be more useful in these circumstances. Successful cardiac transplantation, with or without a left ventricular assist de- vice as a bridging therapy, has been reported in two HIV-positive patients, although the latest report relates to the diagnosis of cardio- myopathy in a subject with a normal CD4 count, undetectable viral Fig. 16.9.3.1 Four chamber dilatation and systolic dysfunction in HIV- positive man with undetectable viral load on HAART.

section 16 Cardiovascular disorders 3536 load, and no history of opportunistic infection. Such treatment is applicable to only a very few HIV patients with heart muscle disease. Although still common in third world countries, the incidence of myocarditis, heart muscle disease, and symptomatic heart failure appears to have decreased in the HAART era, although reports of diastolic dysfunction possibly associated with hypertension and age are increasing. Right ventricular dysfunction and pulmonary hypertension in HIV/AIDS Right ventricular dysfunction may occur as part of HIV heart muscle disease but can occur in isolation, without pulmonary hyperten- sion, and is of unknown significance. Bronchopulmonary infections should be treated aggressively, and intravenous drug use—which may result in microvascular emboli—should be discouraged. Isolated pulmonary hypertension is a rare, noninfective com plication of HIV infection and has a grave prognosis, with a 50% survival at 1 year (Fig. 16.9.3.3). It is prevalent in sub-Saharan Africa and other developing countries. HAART has had no impact on the incidence of this devastating condition, which has little cor- relation with CD4 counts and may be related to the action of viral proteins or cytokines on the endothelial cell. Characteristic patho- logical lesions including intimal fibrosis and plexiform lesions con- firm its similarity to non-HIV primary pulmonary hypertension. Right heart catheterization may be worthwhile to determine if pul- monary hypertension is reversible. Oxygen, calcium channel ant- agonists, vasodilators, phosphodiesterase V inhibitors, and nitric oxide therapy may be considered, but are unproven therapies in this circumstance and do not necessarily improve prognosis. Coronary artery disease in HIV infection HIV lipodystrophy is an ill-defined syndrome that resembles the non-HIV metabolic syndrome and includes dyslipidaemia and in- sulin resistance. Although it is dependent on the type and duration of antiretroviral therapy, and can be found in up to 35% of patients after 12 months of protease inhibitor therapy, it has also been sug- gested that HIV itself is a proatherogenic virus with specific effects on cellular cholesterol management. The significant changes in lipid metabolism noted in the recipi- ents of protease inhibitors make it likely that HIV/AIDS patients are at risk of premature atherosclerosis, and observational studies sug- gest they have an almost twofold increase in the risk of coronary disease compared to non-HIV controls. Acute myocardial infarction appears to be the commonest presentation of coronary heart disease in HIV populations and it is plausible that—because acute coronary 1.00 0.75 0.50 Probability of survival 0.25 0 1.00 0.75 0.50 Probability of survival 0.25 0 0 200 400 600 800 1000 1200 1400 Days Normal Right ventricular dysfunction Left ventricular dysfunction Dilated cardiomyopathy Fig. 16.9.3.2 Top: Survival curves for 296 patients who were
HIV-positive with structurally normal hearts or cardiac dysfunction. Bottom: Survival time to death related to AIDS in 81 subjects with CD4 cell count less than 20 × 106/litre. Reproduced from BMJ, Currie PF, et al., 309, 1605–7. Copyright (1994) with permission from BMJ Publishing Group Ltd. (a) (b) Fig. 16.9.3.3 (a) Long-axis and (b) short-axis parasternal view of a two-dimensional echocardiogram from an HIV-positive intravenous drug user with idiopathic pulmonary hypertension illustrating dilatation of the right ventricle and flattening of the interventricular septum. LV, left ventricle; RV, right ventricle.

16.9.3 Cardiac disease in HIV infection 3537 syndromes involve low-volume, lipid-rich plaques—HAART may promote development of vulnerable lesions or influence plaque rup- ture. Similarly, most HIV patients with coronary disease will have a long duration of HIV infection, which raises the possibility that op- portunistic infections may also be involved in this process. A case of coronary arteritis due to HIV has been described, but acute coronary events are not clearly related to HIV replication as one-third of pa- tients have undetectable plasma HIV-RNA at the time of

symptoms. Coronary angiography can be carried out safely in patients with HIV and frequently reveals proximal vessel involvement and single vessel disease. Percutaneous coronary intervention is a reason- able therapy, with use of drug-eluting stents advocated by some because of concerns over the possibility of aggressive restenosis. Fibrinolysis and coronary artery bypass have also been used with acceptable survival rates, hence it is reasonable that the clinical situ- ation should determine the use of coronary treatments in the same manner as for the non-HIV population. However, care is required over the choice of antiplatelet agents in acute coronary syndromes. The nonnucleoside reverse transcriptase inhibitor etravirine inhibits CYP2C19 and can reduce the antiplatelet activity of clopidogrel and ticagrelor, the coprescription of these drugs is not recommended. Prasugrel may be a suitable alternative antiplatelet agent for use in these circumstances. It may be necessary to consider drug treatment for hyperlipid- aemia, particularly if antiretroviral treatment cannot be changed or interrupted. Like protease inhibitors, most HMG CoA reductase inhibitors (statins) are metabolized through the cytochrome P450 system. Coprescription of these drugs may therefore result in com- petitive inhibition, significantly increased plasma statin levels, and increased risk of myopathy and rhabdomyolysis (Table 16.9.3.2). Pravastatin is metabolized by a different pathway and for this reason it is recommended that hypercholesterolaemia in HIV patients re- ceiving protease inhibitors is initially treated with pravastatin 20 mg daily, with careful monitoring of virological parameters and creatine kinase levels. Rosuvastatin, a more powerful statin metabolized in a similar manner, may only be used in low dose. Fibrates are useful for the treatment of hypertriglycerides. Bile acid sequestrants, although attractive from the point of view of drug interactions, may have ad- verse effects on serum triglyceride levels or impair absorption of antiretrovirals and should be avoided. Ezetimibe may be considered for combination therapy or alone in cases of statin intolerance. Sudden death, cardiac arrhythmia, and stroke Sudden death due to cardiac rhythm abnormalities is well recognized in HIV infection and may be secondary to other cardiac pathology or be a consequence of some forms of treatment. Atrial fibrillation is becoming more common as the HIV population is now ageing. It can be found in 2.6% of patients and caution is required as there are important interactions between anticoagulants, antiarrhythmics, and HAART (see https://www.hiv-druginteractions.org/). Stroke has also emerged as a relatively common event in young HIV patients treated with HAART, with both ischaemic stroke and intracranial haemorrhage being described. Apart from traditional risk factors, HIV-RNA viral load may be an important predictor for ischaemic stroke, while the potential effect of HAART is less clear. Cardiovascular assessment of the patient with HIV/AIDS Echocardiography Echocardiography can easily identify many cardiac conditions common in HIV-positive patients, providing useful information on the appearance of the right ventricle, an indirect assessment of pulmonary pressures, and regional wall motion abnormalities sug- gestive of coronary artery disease. Any HIV-positive patient at high risk of developing cardiovascular disease, or with any potential clin- ical manifestation of it, should therefore have an echocardiogram performed, with repeated imaging every 1 to 2 years. It may be jus- tifiable to perform a baseline study at the time of diagnosis of HIV in any patient, with further examination and closer monitoring on Table 16.9.3.2 Lipid-lowering therapy in HIV infection Drug Indication Statin dose adjustment with HIV therapy PI NNRTI Statin Atorvastatin Pravastatin Rosuvastatin Simvastatin ↑↑LDL – first choice ↑LDL+↑TG – first choice Start with low dose Consider high dose Start with low dose Contraindicated May require high dose May require high dose Start with low dose May require high dose Fibrates ↑↑TG+↑LDL – first choice No reported interaction No reported interaction Ezetimibe Coprescription with statin Statin intolerance No reported interaction No reported interaction Fish oil ↑TG – second choice No reported

interaction No reported interaction PCSK9 Inhibitors Evolocumab Alirocumab ↑↑LDL – under specialist advice No reported interaction No reported interaction ↑↑TG – Triglyceride >5.6 mmol/litre ↑↑LDL – LDL >4.9 mmol/litre ↑LDL – LDL >3.4 mmol/litre NNRTI – nonnucleoside reverse transcriptase inhibitor; PI – protease inhibitor.

section 16 Cardiovascular disorders 3538 discovery of cardiovascular abnormalities or in those with signifi- cant viral infection or unexplained pulmonary symptoms. Assessment of cardiovascular risk Traditional cardiovascular risk profiling has become more im- portant in the care of HIV-positive patients. The prevalence of heavy cigarette smoking in HIV-infected patients is as high as 40%. Diabetes mellitus requiring treatment is common, and HIV patients appear to be at higher risk of developing hypertension at a younger age than the general population, such that blood pressure screening is recommended. A careful history should also identify a family his- tory of premature vascular disease, recreational drug use, poor diet, and lack of physical exercise. A risk score may be calculated to help guide investigation and treatment (Fig. 16.9.3.4), but it may also be useful to consider HIV infection and HAART in themselves as spe- cific risk factors for premature atherosclerosis. FURTHER READING Balloca F, et al. (2017). Cardiovascular disease in patients with HIV. Trends Cardiovasc Med, 27, 558–63. Calabrese LH, et al. (2003). Successful cardiac transplantation in an HIV-1-infected patient with advanced disease. N Engl J Med, 348, 2323–8. Cecchia EJ, et al. (2007). Infective endocarditis in drug addicts: role of HIV infection and the diagnostic accuracy of Duke criteria.
J Cardiovasc Med, 8, 169–75. Cerrato E, et al. (2013). Cardiac dysfunction in pauci symptomatic human immunodeficiency virus patients: a meta-analysis in the highly active antiretroviral therapy era. Eur Heart J, 34, 1432–6. Currie PF, et al. (1994). Heart muscle disease related to HIV infec- tion: prognostic implications. BMJ, 309, 1605–7. D'Ascenzo F, et al. (2012). Acute coronary syndromes in human im- munodeficiency virus patients: a meta-analysis investigating adverse event rates and the role of antiretroviral therapy. Eur Heart J, 33, 875–80. D'Ascenzo F, et al. (2015). A meta-analysis investigating incidence and features of stroke in HIV-infected patients in the highly active anti- retroviral therapy era. J Cardiovasc Med, 16, 839–43. DAD Study Group (2008). Use of nucleoside reverse transcriptase in- hibitors and risk of myocardial infarction in HIV-infected patients enrolled in the DAD study. Lancet, 371, 1417–26. Holloway CJ, Boccara F (2017). HIV-related cardiovascular disease: closing the gap in mortality. Curr Opin HIV AIDS, 12, 509–12. Hsue PY, Waters DD (2005). What a cardiologist needs to know about patients with human immunodeficiency virus infection. Circulation, 112, 3947–57. Janda S, et al. (2010). HIV and pulmonary arterial hypertension: a sys- tematic review. HIV Med, 11, 620–34. Jarrett H, Barnett C (2017). HIV-associated pulmonary hypertension. Curr Opin HIV AIDS, 12, 566–71. Knudsen A, et al. (2013). Angiographic features and cardiovas- cular risk factors in human immunodeficiency virus-infected patients with first-time acute coronary syndrome. Am J Cardiol, 111, 63–7. Krishan K, et al. (2012). Successful left ventricular assist device bridge to transplantation in a patient with end-stage heart failure and human immunodeficiency virus. Artif Organs, 36, 759. Nahass RG, et al. (1990). Infective endocarditis in intravenous drug users: a comparison of human immunodeficiency virus type 1– negative and positive patients. J Infect Dis, 162, 967–70. Rogers JS, et al. (2008). Immune reconstitution inflammatory syn- drome and human immunodeficiency virus-associated myocarditis. Mayo Clin Proc, 83, 1275–9. Sliwa K, et al. (2012). Contribution of the human immunodeficiency virus/acquired immunodeficiency syndrome epidemic to de novo presentations of heart disease in the Heart of Soweto Study Cohort. Eur Heart J, 33, 866–74. Stein JH, et al. (2014). Arterial disease in patients with human im- munodeficiency virus infection. J Am Coll Cardiol lmg, 7, 515–25. Volberding PA, et al. (2003). The Pavia consensus statement. AIDS, 17

Suppl 1, S170–9. LOW RISK: <50 yrs, normotensive, nonsmokers, no history of diabetes, dyslipidaemia or coronary heart disease. No family history of cardiovascular disease, normal BMI. MODERATE RISK: >50 yrs, history of lipodystrophy, impaired glucose tolerance, diabetes, hypertension, dyslipidaemia. Family history of cardiovascular disease, smokers, on HAART, increased BMI HIGH RISK: As above with history of coronary artery or other vascular disease Fasting lipid profile Fasting blood sugar As above, plus regular fasting lipid profile, standard oral glucose tolerance test. Consider cardiological involvement. Consider resting and exercise electrocardiography and echocardiography in individual cases As above, plus consider noninvasive or invasive assessment in each individual case PATIENT CHARACTERISTICS CARDIOVASCULAR INVESTIGATIONS Fig. 16.9.3.4 An approach to cardiovascular assessment in patients with HIV.

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