SAJS
Vascular Surgery: Review

Other manifestations of HIV vasculopathy

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Summary

Descriptions of the numerous manifestations of human immunodeficiency virus (HIV) infection affecting almost every organ system have abounded in recent publications. Multiple radiological, clinical and postmortem reports have recorded the cerebral, pulmonary, cardiac, renal, rheumatological and gastrointestinal pathologies in HIV-infected individuals, ranging from the bizarre to the mundane. Large-vessel HIV-related vascular manifestations have previously been reported in the surgical literature. We describe and review the manifestations of HIV-associated vasculopathy as it pertains to the cerebral, cardiovascular, mesenteric and renal circulations.

Since the first descriptions of acquired immune deficiency syndrome (AIDS) in homosexual men in San Francisco in 1981, HIV has commonly been associated with and implicated in the pathogenesis of vascular disease. The South African experience of HIV-related aneurysms occurring in young HIV-infected individuals suggested a distinct clinicopathological entity, based on distribution, morphological description and histopathological findings.[1,2]

Less convincing, but occurring more frequently in younger HIV-infected South Africans, has been an apparently unique type of vascular occlusive disease.[3] This has generally been encountered in those individuals with advanced disease and significant immunocompromise. These manifestations are not unique to South Africa, and have also been described elsewhere.[4]

Although many reports preceded the highly active antiretroviral treatment (HAART) era, they still occur in areas where HAART is not available. Very few descriptions of HIV-associated vasculopathy in other sites, such as the cerebral, coronary, renal or mesenteric territories, have been reported in the surgical literature. This is understandable, considering that much of the pathology manifests as systemic vasculitides, with very limited surgical treatment options. Systemic vasculitides, however, have been reported in less than 1% of HIV patients, predominantly affecting skin, muscle and nerves and very rarely other organ systems.

The advent of HAART has dramatically modified outcomes in HIV/AIDS, with concerns now being expressed about the older HIV population group exposed to long-term HAART now being more susceptible to precocious and/or accelerated atherosclerotic vascular disease.

The aetiology of vasculopathy in HIV-infected individuals has been widely debated, and is probably multifactorial. For practical purposes HIV vasculopathy may be classified as:

- HIV-related vasculitis
- HIV/HAART-related atherosclerotic vascular disease
- mixed (both pathologies occurring in the same patient).

HIV-related vasculitis can further be subclassified into four types:[5]

Type I: Vasculitides that are well described in the non-HIV population group but occur coincidentally in HIV-infected individuals (Takayasu's disease, Behçet's disease, giant cell arteritis, polyarteritis nodosa, etc.).

Type II: Drug-associated vasculitis (abacavir, nevirapine, effavirenz, trimethoprim/sulphamethoxazole, etc.).

Type III: Vasculitis-associated with known infections (cytomegalovirus, hepatitis B, hepatitis C, *Toxoplasma gondii*, etc.).

Type IV: Vasculitis probably associated with HIV aetiology (primary angiitis of the central nervous system (CNS), Kawasaki-like syndromes, non-hepatitis B polyarteritis nodosa, HIV-related aneurysms, etc.).

Cerebrovascular disease

HIV and stroke

Neurological disorders are not uncommon in patients with HIV-1 infection. Postmortem studies have shown that involvement of the CNS is estimated to occur in between 70% and 90% of HIV-infected patients. Approximately 10 - 20% of HIV-infected patients present with neurological symptoms as a first manifestation.[6,7]

Multiple pathologies contribute to the aetiology of stroke in HIV-1-infected patients. The vast majority are associated with CNS infections and/or tumours. Only a small proportion are related to vascular pathology directly attributable to or associated with the HIV infection itself.[8]

Overall, clinical neurological manifestations occur in up to 40% of patients with AIDS, but stroke is thought to occur in as few as 1.3% of cases, although the true incidence of stroke in HIV patients is not accurately known. HIV-positive patients with strokes generally have a poor survival (mean of ~4 months).

Cerebral infarction rates range from 6% to 34% in autopsy series, but few have clinical correlation. In one review of 6 clinical series, the stroke prevalence ranged from 0.5% to 34%.[9] A cohort study of 772 HIV-positive patients reported a 0.8% prevalence for transient ischaemic attacks (TIA) and 1.2% for stroke, with an estimated annual incidence rate of

216 per 100 000. The prevalence was highest in the more advanced form of the disease.[10]

In another clinical review of 1 600 HIV patients, Pinto found an incidence of 0.75%, which was higher than the risk of stroke in a comparable HIV-negative group (0.025%). In an autopsy review of 763 patients only 1.3% of HIV-infected patients had a stroke syndrome. Pathologically detected ischaemic infarcts were more common (68%).[7]

Connor *et al.*, in an autopsy study excluding other aetiologies associated with stroke in HIV-positive cases, found only 1 TIA recorded clinically in 10 cases (of a total of 183 autopsies) with cerebral infarcts directly attributable to HIV vasculopathy.[11]

Numerous autopsy, radiological and clinical studies suggest an association between stroke and HIV infection related to vascular pathologies, coagulopathies or cardio-embolism. HIV-related vasculopathy has generally been described in association with co-infections in HIV-infected patients.

In a recent study, Mochan *et al.* analysed 35 HIV, HAART-naïve patients with stroke using CT imaging.[12] They found cerebral infarction in 33 (94%) and intracerebral haemorrhage in 2 (6%). In 31 patients the infarcts occurred in the distribution of the anterior circulation. Conventional cerebral angiography, performed in 22 patients, was normal in 15. The seven patients revealed: arterial thrombosis in 3 patients (internal carotid artery in 2, middle cerebral artery in 1, diffuse intracranial vasculopathy with multiple stenotic lesions involving small and medium-size vessels in 2 cases, low-grade carotid bifurcation stenosis in 1 case, and extracranial internal carotid artery dissection in 1 case. In their analysis, 10 patients had more than 1 underlying cause for the stroke, including meningitis (25%), potential cardioembolic cause (9%), coagulopathy (49%) and hypertension (2 patients). Only 4 patients had a stroke directly attributable to HIV-related vasculopathy or vasculitis (with varicella zoster co-infection in 1 case).

HIV-related cerebral vasculitis has generally been associated with CNS infections, lymphoproliferative disorders or drugs.

There are 2 South African retrospective, case-controlled studies comparing stroke rates in young patients (age under 46 years). Hoffman *et al.* compared 22 HIV-positive, HAART-naïve, stroke patients with 22 HIV-negative controls with stroke.[13] The distributions of infarcts were similar in both groups on CT or MR imaging and micro-infarcts were not documented in either group. Conventional angiography (not done in all cases) demonstrated more internal carotid artery and middle cerebral artery occlusions in the HIV group than in the control group. Classic risk factors for stroke were infrequent in the HIV group. Patel *et al.* reviewed 293 black patients aged between 15 and 44 years with stroke (245 cerebral infarctions and 48 haemorrhages).[14] There were 56 HIV-positive, HAART-naïve patients (51 with cerebral infarction and 5 with cerebral haemorrhage). No specific aetiology was found in 68.9% of the cases. There was no difference in cardioembolic aetiology between the groups. Conventional angiograms were performed in 158 patients, of which 62% were positive. There was no statistical difference in the number of internal carotid artery (ICA) or middle cerebral artery (MCA) occlusions between the groups, although there was a trend towards more ICA and MCA occlusions in the HIV group.

Tipping *et al.* reviewed 67 HIV-positive patients (of which 61 patients were under 45 years of age).[15] Cerebral infarction occurred in 96% (64 patients) and intracerebral haemorrhage in 4%. HIV-positive patients did not have classic risk factors for stroke. A distinct aetiology for stroke was identified in 81% of patients: infections (28%), coagulopathy (19%), cardioembolism (14%), unknown (19%) and HIV-associated vasculopathy (20%). Occlusion of the common carotid artery (CCA) or ICA was demonstrated in 7 (11%) patients. Autopsy findings in 1 patient revealed thrombotic occlusion of the right carotid artery. Sections of the carotid bifurcation revealed adventitial fibrosis and neovascularisation, intimal fibrosis, fragmentation of the internal elastic lamina, medial degeneration and lymphoplasmacytic infiltrate. Six patients (9%) had intracranial vascular pathology not associated with any other aetiology for stroke. Angiography revealed medium vessel occlusion, with or without ectasia, and areas of vascular stenoses involving the circle of Willis and cerebral arteries including their proximal divisions.

In the Edinburgh HIV autopsy cohort, 10 cerebral infarcts (of a total of 183 cases with cerebral infarcts) were ascribed to HIV vasculopathy.[11] Histopathology of the intracranial vessels revealed intimal thickening, dilatation of the perivascular spaces with areas of pigment deposition, microvessel mineralisation and perivascular inflammatory cells. Interestingly, no vasculitis (arterial wall inflammatory infiltrate) was found. The authors suggest an exhaustive search for stroke aetiology before ascribing it to HIV vasculopathy.

Many of the studies evaluated stroke in HIV-positive patients not receiving HAART. In a recent study, Ortiz *et al.* evaluated 82 HIV-positive patients.[16] Forty-eight patients (58%) were on HAART. Seventy-five patients (92%) had a diagnosis of HIV prior to the stroke. Among the 77 patients who had ischaemic strokes, 10 had atherosclerosis involving large arteries (4 CCA/ICA, 5 MCA and 1 vertebrobasilar stenoses). Fifteen patients (19%) had small-vessel occlusion confirmed on imaging studies. Other aetiologies included vasculitis in 10 (23%), vertebral artery dissection in 1, coagulopathy in 7 and a potential cardioembolic source in 15. Classic risk factors were present: tobacco smoking (51%), hypertension (42%) and diabetes mellitus (7%). Interestingly, hyperlipidaemia was uncommon. Patients with atherothrombotic strokes were older (45.3 versus 40.1 mean age) than those with non-atherothrombotic strokes. Sixty-eight per cent of patients with atherothrombotic strokes had received HAART. However, the use of HAART did not correlate with the type of ischaemic stroke.

Stroke due to co-viral vasculitis in HIV-positive patients has been described. These patients usually present with advanced HIV infection. Varicella zoster vasculitis (VZV) associated with stroke has been described following zoster ophthalmicus and zoster oticus. Zoster vasculitis is a granulomatous vasculitis with multinucleate giant cells, viral antigens, viral DNA and Cowdry A inclusions seen in arterial walls. Diagnosis is usually accomplished by lumbar puncture with cerebrospinal fluid (CSF) analysis and serology. Ortiz *et al.* described a case associated with the Ramsay Hunt syndrome in which MRI demonstrated a pontine infarct.[17] There were multiple stenotic areas involving distal vertebral and basilar arteries, as well as the arteries related to the circle of Willis on MRI and conventional angiography. Treatment consists of gancyclovir, prednisone and HAART.

Primary angiitis of the CNS (PACNS), first described in 1959, is an uncommon vasculitis predominantly involving

small and medium intracerebral arteries and veins, including leptomeningeal vessels.[18,19] It may be associated with immunocompromise, and has been documented in HIV-infected patients with stroke. Diagnosis is based on neuroimaging, CSF analysis, and exclusion of current infection and other CNS pathology on screening. Nogueras *et al*. reported a case of recurrent strokes with primary angiitis of the CNS in an HIV-infected patient.[19] MRA findings of segmental stenoses involving the distal ICA and basilar arteries were documented, with marked luminal narrowing. Histopathological findings documented lymphocytic vasculitis of the basal meningeal and parenchymal vessels. A fibrous vasculitis was found in vessels of the circle of Willis with intimal fibrosis, medial destruction and lymphoplasmacytic infiltrate with multinucleated giant cells. PACNS generally had a poor prognosis, most cases being reported in autopsy series. Whether HAART will alter the incidence or prognosis with PACNS remains speculative.

Stroke secondary to spontaneous artery dissection in HIV-infected patients has been reported.[12,16] Felicio *et al*. reported a case in an HIV-infected patient with Wallenberg's syndrome (ipsilateral cerebellar infarct) secondary to a vertebral artery dissection.[20] The patient was anticoagulated with documented neurological improvement.

Stroke secondary to CCA/ICA atherosclerotic plaques has been well studied in HIV-negative patients. Carotid endarterectomy and carotid angioplasty with stenting, both currently indicated in treating significant carotid stenoses, have played a major role in reducing stroke. Studies have indicated an increasing incidence of cardiovascular and cerebrovascular disease in the HAART era. Currently there does not appear to be an increasing incidence of stroke associated with carotid bifurcation plaques in HIV-infected patients in the HAART era. Regina *et al*. reported 2 patients with asymptomatic high-grade ICA stenosis of approximately 80%, with carotid duplex showing progressive stenosis in both patients.[21] Both CCA and external carotid arteries (ECA) were normal. Both were young patients (<40 years). Both were on long-standing HAART including a protease inhibitor (PI). At surgery, both the lesions were found to be focal, thick, fibrotic ICA plaques with no endarterectomy plane. A resection of the proximal ICA with reimplantation to the ECA was performed in both. Histology revealed an intimal lesion with fibro-fatty plaque, fragmentation of the internal elastic lamina, medial scarring and occasional perivascular lymphocytes around the vasa vasorum. A lymphoplasmacytic infiltrate was found in the intima and media. HIV-1 was isolated from biopsy specimens.

HIV and cerebral aneurysms

HIV-related intracranial aneurysms have been described in paediatric[22-24] and, more recently, adult populations. Dubrovsky *et al*. reported on 5 paediatric cases and reviewed an additional eight paediatric cases from the literature.[25] Seven patients acquired the HIV infection perinatally. Postmortem findings were described in 4 patients. All had ectasia and aneurysms confined to the large arteries of the circle of Willis. The consistent histological findings were intimal thickening, destruction of the internal elastic lamina, loss of muscularis and medial fibrosis. The latency period to diagnosis ranged from 2 years to 11 years, with poor survival following diagnosis (mean <6 months). They postulated VZV infection and HIV as possible aetiological agents. HIV protein and genome was isolated in 2 of the postmortem cases.

Patsalides *et al*. reviewed 426 HIV-positive paediatric patients, who all had neuroimaging studies.[22] Eleven patients (2.6%), 6 of whom were males, were found to have cerebrovascular lesions. Seven patients had no neurological symptoms and only 1 had a stroke. Vertical transmission of the HIV infection occurred in 7 patients. Multiple aneurysms (total of 26 aneurysms) were documented in 7 patients, 4 with associated cerebral infarcts. Twenty aneurysms involved the anterior circulation. Twenty-four aneurysms were fusiform. Four of the 7 patients had multiple aneurysms. Twenty-seven cerebral infarcts were seen in 8 patients, 4 without aneurysms. Seven cerebral infarcts were cortical and 20 involved the basal ganglia, 16 infarcts occurring in territories supplied by arteries associated with aneurysms. Co-infection with VZV was seen in 45% (5/11). All patients had advanced HIV disease (CD4 counts less than 200 cells/µl) Histopathological findings in 1 patient were similar to those reported by Dubrovsky *et al*.

HIV-related cerebral aneurysms complicated by symptomatic ischaemic infarcts have been described as part of the immune-reconstitution inflammatory syndrome (IRIS).[23] An immune-mediated vasculitis is thought to be the basis of IRIS in response to improved immunocompetence with HAART, generally after less than 1 year of therapy. MRA in this case revealed multiple fusiform aneurysms involving the circle of Willis. No other aetiology was found on screening. The patient improved on HAART, acyclovir and aspirin.

Cerebral vasculopathy with aneurysm formation has also been described in young HIV-positive adults.[26-28] Kossorotoff *et al*. described 2 HIV-positive patients with strokes and MCA territory infarcts.[26] MRA revealed multiple fusiform aneurysms, ectasia and stenotic areas involving small and medium-sized arteries. One patient had an ipsilateral thrombosed distal ICA aneurysm. VZV was probably causally related in 1 patient.

Tipping *et al*. described stroke in a 27-year-old female patient with neuroimaging findings of fusiform aneurysmal dilatation of the arteries of the circle of Willis.[27] Autopsy findings revealed fusiform dilatation of left ICA, and left MCA branches. Thrombus was present in the MCA and anterior divisions. Histology of the involved segments revealed intimal fibrosis with hyalinisation, medial atrophy and fragmentation of the elastic lamina. Alcian blue staining showed depositions of mucopolysaccharides in the intima and media.

Subarachnoid haemorrhage (SAH) has been described in association with HIV-related cerebral aneurysms in adults. Hamilton *et al*. reported a 34-year-old HIV-positive male on HAART (CD4 count 66 cells/µl) with end-stage renal failure, cardiomyopathy and left-sided weakness.[29] CTA demonstrated an SAH with multiple fusiform and giant saccular aneurysms. He was treated expectantly. Taylor *et al*. reported 3 patients with SAH and cerebral aneurysms in young HIV-infected adults with low CD4 counts.[30] They postulated intracranial arterial dissection as the pathogenic process associated with SAH in 2 of their patients. Two of the patients were treated with endovascular techniques: segmental vessel trapping using GDC coils in 1 patient and partial coil embolisation of a false aneurysm in the other (Figs 1 and 2).

Modi *et al*. recently reported 3 cases of HIV-related intracranial aneurysms presenting with cognitive impairment, SAH and seizures respectively.[31] All had multiple fusiform

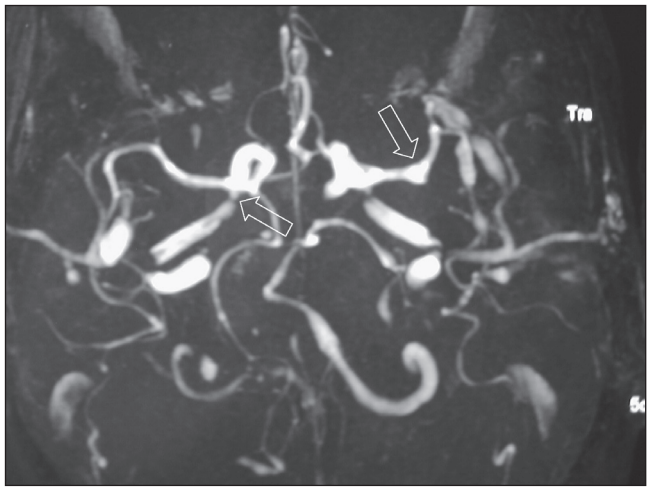

Fig. 1a. Axial view of magnetic resonance angiogram showing multiple irregular central cerebral artery stenoses and dilatations (arrows). (Courtesy Professor Allan Taylor, Division of Neurosurgery, University of Cape Town.)

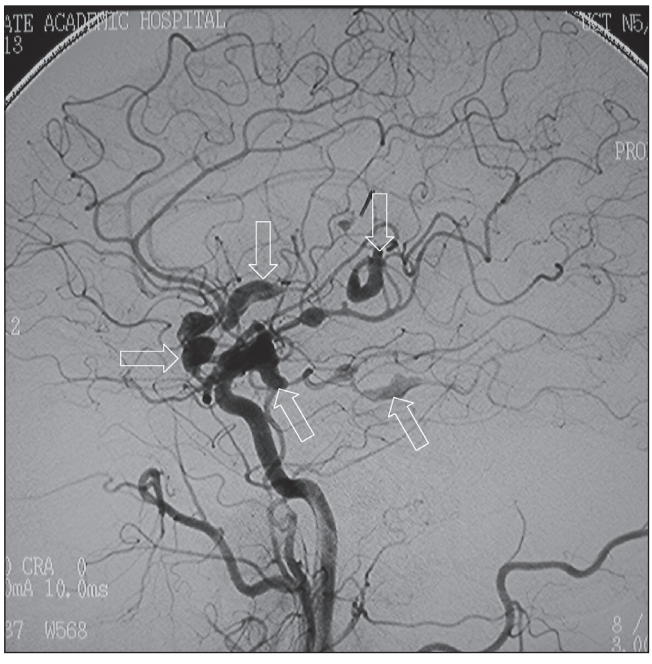

Fig. 1b. Lateral common carotid artery digital subtraction angiogram showing multifocal central cerebral artery irregular stenoses and dilatations (arrows). (Courtesy Professor Allan Taylor, Division of Neurosurgery, University of Cape Town.)

intracranial aneurysms (1 patient thought to have a saccular aneurysm was found to have a fusiform aneurysm at surgery and was not treated). A screen for other aetiology was negative in all 3 cases. On review of the literature, they discovered an additional 11 patients presenting with strokes, headache and SAH, 7 of whom had saccular (probably congenital) aneurysms, with the remainder being fusiform aneurysms.

HIV-related aneurysms occur in young adults (under 45 years) with advanced HIV infection (CD4 count less than 200 cells/μl). Patients are generally HAART-naïve. There is some evidence that HAART to an extent improves the clinical course of HIV-related aneurysms in paediatric patients. Whether HAART will influence outcomes in HIV-related aneurysms in adults is still to be defined. Novel endovascular strategies are now available to treat selected individuals.

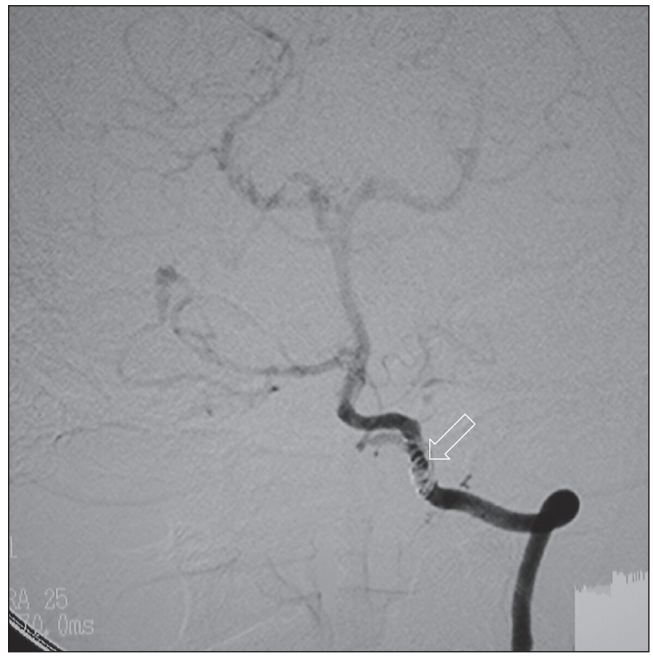

Fig. 2. Vertebral digital subtraction angiogram after coiling (arrow) showing occlusion of side-branch false aneurysms and recanalised vertebral artery. (Courtesy Professor Allan Taylor, Division of Neurosurgery, University of Cape Town.)

HIV and cerebral venous thrombosis

This is a rare manifestation in HIV-infected patients. Meyohas *et al.* reported a case of superior saggittal sinus (SSS) thrombosis in a patient with dual primary infection with HIV and CMV, both viruses known to be associated with vasculitis.[32] The thrombophilia screen was normal. Prendki *et al.* reported SSS and transverse sinus (TS) thrombosis in 2 HIV-infected patients as part of a rapid immune reconstitution inflammatory syndrome (IRIS).[33] Both patients were initially treated for cryptococcal meningitis. One patient subsequently had his HAART regimen revised, while HAART was commenced in the second patient. Both patients developed progressive neurological symptoms following a delay of 1 - 2 months of HAART. MR imaging revealed SSS and TS thrombosis in both patients. Anticoagulation was instituted with variable clinical response.

Cardiovascular disease

Common cardiovascular manifestations in HIV-infected individuals include pericardial effusions, myocarditis, dilated cardiomyopathy, systemic hypertension (up to 74% of HIV-infected patients in the HAART era), HIV-associated pulmonary hypertension and AIDS-related cardiac tumours.[34,35]

HIV and coronary vasculitis

A wide variety of vasculitides unrelated to HIV may affect the coronary arteries, including polyarteritis nodosa, Henoch-Schönlein purpura and drug-induced vasculitis.[35,36] Shingadia *et al.* reported a case of Takayasu`s disease in an HIV-infected adolescent.[37]

Kawasaki-like syndromes have also been reported.[5,38] Kawasaki disease is an acute vasculitic syndrome of unknown aetiology occurring in paediatric patients under 5 years of age. The diagnosis is based on clinical features includ-

ing fever of over 5 days, bilateral conjunctivitis, erythema or swelling of the hands and feet, rash, strawberry tongue and cervical lymphadenitis (lymph nodes greater than 15 mm/non-infectious). Kawasaki disease typically affects small and medium-sized vessels, particularly the coronary arteries. Treatment consists of aspirin and intravenous immunoglobulin. Coronary aneurysms developed in 24.6% (146/594) of paediatric patients in 1 large series.[39] In the acute stage giant aneurysms (over 8 mm in diameter) were seen in 26 patients with conventional angiography. Twelve progressed to stenosis or complete obstruction of the coronary arteries. Myocardial infarction occurred in 8 patients, with 4 deaths. Barbaro *et al*. reported a 32-year-old HIV-infected patient who presented with a myocardial infarct following a flu-like illness 1 week earlier.[40] He had no other cardiovascular risk factors. His CD4 count was 230 cells/µl. Autopsy specimens of the coronary arteries revealed erosion and fissuring of the anterior descending and circumflex arteries. Histology revealed a dense lymphocytic infiltrate with necrosis of the intima. *In situ* hybridisation indicated the presence of HIV-1 in the arterial wall. A follow-up study[5] showed the presence of IgA plasma cells within the vasculitic lesion, a feature apparently unique to paediatric Kawasaki disease. Stankovic *et al*., in a review of the literature, identified 20 HIV-infected patients (17 men) with a Kawasaki-like syndrome.[38] Eighteen patients were on HAART. The majority of patients had low CD4 counts (mean CD4 count was 83 cells/µl). Prognosis was favourable with aspirin and intravenous immunoglobulin. No coronary aneurysms were described owing to lack of coronary imaging in these cases. Interestingly, in a recent review of coronary aneurysms, HIV was not listed in the pathogenesis.[41]

HIV and atherosclerotic coronary artery disease

Cardiology publications have noted the increasing frequency of coronary artery disease (CAD) in HIV-infected patients on HAART.[42] There is still considerable debate regarding the exact aetiology of HIV-related CAD which may be due to HIV, HAART or HAART-associated metabolic syndrome, or a combination thereof. There is agreement that overall HAART has considerably modified outcomes in HIV/AIDS, reducing opportunistic infection, improving life expectancy and quality of life. However, concerns have now been raised regarding premature or accelerated atherosclerotic cardiovascular, cerebrovascular and peripheral arterial disease in the older HIV cohort on longstanding HAART.[43]

The pathogenesis of atherosclerotic CAD is likely to be multifactorial.[44,45] The association between low CD4 counts and CAD has been inconsistent. The dysmetabolic profile of HAART regimens, especially protease inhibitor (PI) based therapies, with increased total cholesterol, increased low-density lipoprotein (LDL), hypertriglyceridaemia, insulin resistance and lipoatrophy/dystrophy, has been implicated.[46-49] HIV-infected patients with classic risk factors for CAD (age, personal or family history, diabetes mellitus, smoking, hyperlipidaemia) on HAART may be at increased risk of CAD.

Mehta *et al*., in a review of 129 HIV-infected patients with CAD (mean age of 42 years) found no correlation between CD4 count and CAD.[50] Acute myocardial infarction (MI) was the initial clinical presentation in 77% of patients. Forty-seven per cent of patients had triple vessel disease (18% had 2 vessel and 35% had 1 vessel disease). In one study mortality associated with a first MI approached 24%.[42] Of concern is the finding that as many as 69% of patients were less than 50 years old.[46,50]

Coronary pathology in these patients has been reported as distinct (diffuse and circumferential intimal thickening, atherosclerotic plaques and unusual proliferation of smooth muscle with luminal protrusions). Some of these features are seen in transplant vasculopathy.[51,52]

Rickerts *et al*., in a retrospective analysis of the Frankfurt HIV Cohort Study, found a fourfold increase in the annual incidence of CAD after the commencement of HAART.[53] Klein *et al*. reported a coronary event rate of 5.5/1 000 patient years in the HAART era, higher than that of a control group.[54] While the relative risk of increase in CAD in HIV-infected patients on HAART approaches 25% per annum, the absolute increase in these patients is small.[46,55]

HIV and HAART have confounded classic cardiac risk evaluation and categorisation. Other models beyond the Framingham score are currently being evaluated.[37] Surrogate markers for the detection of subclinical atherosclerotic CAD are being evaluated (including coronary artery calcium score, high sensitivity C-reactive protein (CRP) and carotid intima medial thickness).[56-59]

Medical therapy for atherosclerotic CAD in these patients is along currently established guidelines. Caution should be exercised in the prescription of pharmaceutical agents, especially lipid-lowering agents metabolised by the same pathway as PIs. Pravastatin, and to a lesser extent atorvastatin, is preferred to simvastatin and lovastatin.[60]

In contradistinction to the large cardiology experience with percutaneous coronary intervention (PCI) in non-HIV patients, the experience with PCI in HIV-infected patients is limited.[61-63] Treatment with percutaneous transluminal coronary angioplasty (PTCA) and coronary stenting (CS) has been described, with promising early outcomes.

Intermediate outcomes with PCI have also been reported. Boccara *et al*. reviewed their experience with 20 HIV-infected patients with acute coronary syndrome.[64] Initially 4 patients received thrombolysis, 2 patients underwent PTCA and 7 had CS. The remainder of the patients were treated medically. At a mean follow-up of 38 months (range 2 - 72 months) 18 cardiovascular events, including 1 death, occurred in 50% of patients. None of the patients with a previous PCI needed target vessel revascularisation (TVR). Two patients had CS and 3 patients had a coronary artery bypass graft (CABG). In a similar case-controlled study, Hsue *et al*. showed similar results.[65] Matetzky *et al*. compared HIV-infected patients with acute MI with a non-HIV control group.[66] At 15 months follow-up the HIV-infected group had a higher incidence of recurrent MI and TVR, independent of type of HAART regimen. Similar findings at 36-month mean follow-up were noted by Escaut *et al*.[67]

Boccara *et al*. evaluated the outcomes of PCI in 50 HIV-infected patients and compared them with 50 non-HIV patients.[68] The procedural success was 98% in each group. Mean follow-up was 625 days. Clinical restenosis, TVR, major adverse cardiovascular event (MACE)-free and MI rates were not significantly different between the groups.

CABG in HIV-patients has been reported in HIV-infected patients with or without HAART. Blyth *et al.* reviewed their experience with cardiopulmonary bypass in 49 HIV-infected, HAART-naïve patients for a range of indications (CABG in 3).[69] The perioperative mortality was 6%, with 34.7% mor-

bidity. Evolving criteria for cardiac surgery in HIV-infected patients at this unit included a CD4 count of over 400 cells/µl and the absence of AIDS. Traciotis *et al*. performed 27 cases of CABG with no perioperative deaths in this subgroup.[70] Freedom from a composite endpoint of angina, death, MI, repeat revascularisation and congestive cardiac failure at 3 years was 81%. Similar results were reported by Castillo *et al*.[71] With a follow-up of 8.2 years, the long-term mortality was 10.8%. Results of a multicentre case-control study, comparing CABG in HIV-infected patients, with CABG in HIV-negative patients have been published recently.[72] Thirty-day outcomes (death, MI, stroke, mediastinitis, and reintervention) were similar in both groups. At follow-up (median: 42 months) MACE was significantly higher in the HIV-infected group (42% v. 25%), predominantly due to the need for PCI of progressive occlusive disease in the native coronary arteries (not graft related).

Visceral HIV-related vasculopathy

Vascular involvement of the mesenteric circulation in HIV-infected individuals is not commonly described.

HIV and mesenteric vasculitis

Polyarteritis nodosa-like syndromes and nonspecific systemic necrotising vasculitis are the commonest vasculitides described in HIV-infected individuals, typically involving skin, muscle and peripheral nerves.[73] Reports of mesenteric or renal involvement are rare compared with classic polyarteritis nodosa (PAN). Coinfection with current hepatitis B in these cases is rarely described. Acute flare-ups are not seen in the HIV population.

Sambatakou *et al.* reported a case of acute mesenteric ischaemia in a 31-year-old HIV-infected, HAART-naïve patient (with CD4 count of 142 cells/µl and viral load of 217.400 copies/ml).[74] Colonoscopy revealed rectal and sigmoid mucosal erosions. The patient underwent a laparotomy with resection of 125 cm of ileum. The diagnosis of mesenteric artery thrombosis was entertained at laparotomy. Histopathology revealed a necrotising vasculitis involving small and medium-sized vessels of the gut, with gut ulceration and ischaemia. A renal biopsy for progressive renal dysfunction revealed IgA deposits in the capillaries (a feature of PAN). He was treated with cyclophosphamide, prednisone and HAART and recovered well.

Cytomegalovirus (CMV) vasculitis occurs in immunocompromised individuals, causing colitis.[75] However, descriptions of CMV colitis in HIV-infected individuals have not paralleled the HIV pandemic.

Acute mesenteric ischaemia has been documented as a complication of treatment.[76] Zaraa *et al*. described acute mesenteric ischaemia in an HIV-infected 44-year-old woman with Kaposi`s sarcoma following treatment with interferon-A2b and the development of the haemolytic uraemic syndrome. Rapid clinical improvement followed withdrawal of interferon.

HIV and chronic mesenteric ischaemia

Mesenteric large-vessel involvement is unusual in HIV-infected individuals. A large case series profiling 92 HIV-related aneurysms in 28 patients identified only 3 visceral aneurysms. All 3 were asymptomatic and always associated with aortic aneurysms. One coeliac artery aneurysm was thrombosed. There were 2 saccular aneurysms and 1 fusiform aneurysm.[1,2]

Chahid *et al*. reported a case series of 14 patients with chronic mesenteric ischaemia treated by percutaneous transluminal angioplasty (PTA) with or without a stent.[77] A 32-year-old female patient with antiphospholipid syndrome was HIV positive, with early-onset mesenteric atherosclerosis. She presented with weight loss and post-prandial pain. She underwent a PTA and stent with a good technical and clinical outcome on follow-up.

Intraparenchymal splenic artery calcification in a branching configuration has been reported in HIV-infected paediatric patients.[78] The significance of this finding remains obscure.

HIV and abdominal venous thrombosis

Portal and splenic vein thrombosis has been rarely reported in HIV-infected individuals.[79-81] Crum-Cianflone *et al*. evaluated 465 HIV-infected patients for venous thrombosis and found 17 patients (3.7%) with 19 thrombotic events.[81] Two were located in the splenic and portal veins. All patients were on HAART. All had identifiable risk factors for venous thrombosis. In their review of the literature, they identified 9 cases of portal vein thrombosis reported in HIV-infected individuals. The pathogenesis of venous thrombosis in HIV-infected patients is probably multifactorial. Indinavir, a PI, has been associated with portal vein thrombosis.[82]

Renal HIV-related vasculopathy

Renal manifestations of HIV include HIV-associated nephropathy (HIVAN), 'collapsing glomerulopathy', IgA glomerulonephritis, microangiopathic nephropathy (haemolytic uraemic syndrome), immune complex (systemic lupus-like) syndrome and mixed cryoglobulinaemic vasculitis.

There is a growing awareness of PAN-like syndromes in HIV-infected patients. PAN-like syndromes in HIV-infected individuals, although less common compared with classic PAN, can also involve the renal circulation. Sagcan *et al*. reported a 29-year-old HIV-positive patient who presented with spontaneous bilateral perirenal haematomas.[83] A renal angiogram showed multiple intraparenchymal microaneurysms typical of PAN. A unilateral nephrectomy was performed and the diagnosis of PAN was confirmed on histology.

Adjunctive treatment invariably includes azathioprine or cyclophosphamide, prednisone and HAART. Prognosis with bilateral spontaneous perirenal haematomas associated with PAN is reported to be poor, with 5 of 9 patients dying within 6 months.[84] Less invasive treatment strategies have evolved to treat ruptured intrarenal aneurysms, including transcatheter embolisation.

HIV-related large-vessel renal artery aneurysm or occlusion is rare. Nair *et al*., in reviewing a large institutional series of HIV-related aneurysms, reported 1 patient with severe hypertension.[1] The 18-year-old patient was found to have a large suprarenal abdominal aortic aneurysm (AAA) with renal involvement and a non-functioning right kidney. She was treated by elective repair of the suprarenal AAA with multiple side-arm grafting to the visceral and left renal arteries. A right nephrectomy was performed. Unfortunately the patient died following acute renal failure secondary to occlusion of the graft to the left renal artery.

Conclusion

Vasculitides, although uncommon in HIV-infected individuals, should trigger an exhaustive screen for other aetiology (including co-infections, lymphoproliferative disease, and autoimmune disorders) before ascribing it to HIV. Whether HAART will alter the incidence of these vasculitides, and the outcomes associated with some of the manifestations, including intracranial aneurysms, remains speculative. Whether an increased roll-out of HAART in less-developed countries will translate into a delayed increased risk of atherosclerotic vascular disease, as expressed in developed countries, remains to be defined. HAART has affected conventional medical management guidelines for established atherosclerotic vascular disease, especially lipid management, in HIV-infected patients, and these adjustments should be incorporated in our current management of these patients.

REFERENCES

1. Nair R, Robbs JV, Naidoo NG, *et al*. Clinical profile of HIV-related aneurysms. *Eur J Vasc Endovasc Surg* 2000; 20: 235-240.
2. Chetty R, Batiteng S, Nair R. Large artery vasculopathy in HIV-positive patients: another vasculitic enigma. *Human Pathology* 2000; 31(3): 374-379.
3. Nair R, Robbs JV, Chetty R, *et al*. Occlusive arterial disease in HIV-infected patients: a preliminary report. *Eur J Vasc Endovasc Surg* 2000; 20: 353-357.
4. Marks C, Kuskov S. Pattern of arterial aneurysms in acquired immunodeficiency disease. *World J Surg* 1995; 19(1): 127-132.
5. Johnson RM, Babarini G, Barbaro G. Kawasaki-like syndromes and other vasculitic syndromes in HIV-infected patients. *AIDS* 2003; 17: S77-S82.
6. McGuire D, So YT. Neurological dysfunction: an overview. In: Cohen PT, Sande MA, Volberding PA, eds. *The AIDS Knowledge Base*. 2nd ed. Boston, Mass: Little Brown & Co, 1994: 5.6 -1 - 5.6-2
7. Pinto AN. AIDS and cerebrovascular disease. *Stroke* 1996; 27(3): 538-543.
8. Berger JR, Harris JO, Gregorios J, Noremberg M. Cerebrovascular disease in AIDS: a case controlled study. *AIDS* 1990; 4: 239-244.
9. Rabinstein AA. Stroke in HIV-infected patients: a clinical perspective. *Cerebrovasc Dis* 2003; 15: 37-44.
10. Evers S, Nabavi D, Rahmann A, *et al*. Ischaemic cerebrovascular events in HIV infection: a cohort study. *Cerebrovasc Dis* 2003; 15: 199-205.
11. Connor MD, Lammie GA, Bell JE, *et al*. Cerebral infarction in adult AIDS patients: observations from the Edinburgh HIV autopsy cohort. *Stroke* 2000; 31: 2117-2126.
12. Mochan A, Modi I, Modi G. Stroke in black South African HIV-positive patients: a prospective analysis. *Stroke* 2003; 34: 10-15.
13. Hoffman M, Berger JR, Nath A, Rayens M. Cerebrovascular disease in young HIV-infected black Africans in the KwaZulu-Natal province of South Africa. *J Neurovirol* 2006; 6: 229-236.
14. Patel VB, Sacoor Z, Francis P, *et al*. Ischaemic strokes in young HIV-positive patients in KwaZulu-Natal, South Africa. *Neurology* 2005; 65: 759-761.
15. Tipping B, de Villiers L, Wainwright H, *et al*. Stroke in patients with human immunodeficiency virus infection. *J Neurol Neurosurg Psychiatry* 2007; 78: 1320-1324.
16. Ortiz G, Koch S, Romano JG, *et al*. Mechanisms of ischaemic strokes in HIV-infected patients. *Neurology* 2007; 68: 1257-1261.
17. Ortiz GA, Koch S, Forteza A, Romano J. Ramsay-Hunt syndrome followed by multifocal vasculopathy and posterior circulation strokes. *Neurology* 2008; 70; 1049-1051.
18. Chetty R. Vasculitides associated with HIV infection. *J Clin Pathol* 2001; 54: 275-278.
19. Nogueras C, Sala M, Sasal M, *et al*. Recurrent stroke as a manifestation of primary angiitis of the central nervous system in a patient with human immunodeficiency virus. *Arch Neurol* 2002; 59: 468-573.
20. Felicio AC, Silva GS, Dos Santos WAC, *et al*. Spontaneous artery dissection in a patient with immunodeficiency virus infection. *Arq Neuro-Qsiquiatr* 2006; 64(2A): 306-308.
21. Regina G, Ompedovo G, Angiletti D, *et al*. Surgical experience with carotid stenosis in young HIV1 positive patients under antiretroviral therapy: an emerging problem? *Eur J Vasc Endovasc Surg* 2005; 29(2): 167-170.
22. Patsalides AD, Wood LV, Atac GK, *et al*. Cerebrovascular disease in HIV infected pediatric patients: neuroimaging findings. *AJR* 2002; 179: 999-1003.
23. Bonkowski JL, Christenson JC, Nixon GW, Pavia AT. Cerebral aneurysms in a child with acquired immunodeficiency syndrome during rapid immune reconstitution. *J Child Neurol* 2002; 17: 457-460.
24. Mahadevan A, Tagore R, Siddappa NB, *et al*. Giant serpentine aneurysm of vertebrobasilar artery mimicking dolichoectasia – an unusual complication of pediatric AIDS. Report of a case with review of the literature. *Clin Neuropathol* 2008; 27(1): 37-52.
25. Dubrovsky T, Curless R, Scott G, *et al*. Cerebral aneurysmal arteriopathy in childhood AIDS. *Neurology* 1998; 51: 560-565.
26. Kossorotoff M, Touze E, Godon-Hardy S, *et al*. Cerebral vasculopathy with aneurysm formation in HIV infected young adults. *Neurology* 2006; 66: 1121-1122.
27. Tipping B, de Villiers L, Candy S, Wainwright H. Stroke caused by human immunodeficiency virus-associated intracranial large-vessel aneurysmal vasculopathy. *Arch Neurol* 2006; 63: 1640-1642.
28. O`Charoen P, Hesselink JR, Healy JF. Cerebral aneurysmal arteriopathy in an adult patient with acquired immunodeficiency syndrome. *Am J Neurorad* 2007; 28: 938-939.
29. Hamilton DK, Kassel NF, Jensen ME, Dumont AS. Subarachnoid haemorrhage and diffuse vasculopathy in an adult infected with HIV. *J Neurosurg* 2007; 106: 478-480.
30. Taylor A, LeFeuvre D, Levy A, Candy S. Arterial dissection and subarachnoid haemorrhage in human immunodeficiency virus-infected patients. *Interventional Neurorad* 2004; 10: 137-143.
31. Modi G, Ranchod K, Modi M, Mochan A. Human immunodeficiency virus associated intracranial aneurysms: report of three adult patients with an overview of the literature. *J Neurol Neurosurg Psychiatry* 2008; 79(1): 44-46.
32. Meyohas MC, Roullet E, Rouzioux C, *et al*. Cerebral venous thrombosis and dual primary infection with human immunodeficiency virus and cytomegalovirus. *J Neurol Neurosurg Psychiatry* 1989; 52: 1010-1011.
33. Prendki V, Dumas J, Claire B, *et al*. Cerebral thrombophlebitis as a paradoxical reaction in HIV patients. *AIDS* 2008; 22(11): 1384-1385.
34. Ntsekhe M, Hakim J. Impact of human immunodeficiency virus infection on cardiovascular disease in Africa. *Circulation* 2005; 112: 3602-3607.
35. Barbaro G. Cardiovascular manifestations of HIV infection. *Circulation* 2002; 106: 1420-1425.
36. Barbaro G, Fisher SD, Lipschultz SE. Pathogenesis of HIV-associated cardiovascular complications. *Lancet Infect Dis* 2001; 1: 115-124.
37. Shingadia D, Das L, Klein-Gitelman M, *et al*. Takayasu`s arteritis in a human immunodeficiency virus infected adolescent. *Clin Infect Dis* 1999; 29: 458-459.
38. Stankovic K, Miailhes P, Bessis D, *et al*. Kawasaki-like syndromes in HIV-infected adults. *J Infection* 2007; 55: 488-494.
39. Kato H, Sugimura T, Akagi T, Sato N. Long-term consequences of Kawasaki disease. *Circulation* 1996; 94: 1379-1385.
40. Barbaro G, Barbarini G, Pellicelli AM. HIV-associated coronary arteritis in a patient with fatal myocardial infarction. *N Engl J Med* 2001; 344(2): 1799-1800.
41. Cohen P, O`Gara PT. Coronary artery aneurysms: a review of the natural history, pathophysiology and management. *Cardiol Rev* 2008; 16(6): 301-304.
42. D.A.D study group. Cardio- and cerebrovascular events in HIV infected persons. *AIDS* 2004; 18: 1811-1817.
43. D.A.D study group. Modelling the 3 year risk of myocardial infarction among participants in the data collection on adverse events of anti-HIV (DAD) study. *HIV Medicine* 2003; 4: 1-10.
44. Dube MP, Lipschultz SE, Fichtenbaum CJ, *et al*. Effects of HIV infection and antiretroviral therapy on the heart and vasculature. *Circulation* 2008; 118: 36-37.
45. Mu H, Chai H, Lin P, *et al*. Current update on HIV-associated vascular disease and endothelial dysfunction. *World J Surg* 2007; 31: 632-643.
46. Khunnawat C, Mukerji S, Havlichek D, Touma R. Cardiovascular manifestations in human immunodeficiency virus-infected patients. *Am J Cardiol* 2008; 102: 635-642.
47. Barbaro G. Highly active antiretroviral therapy-associated metabolic syndrome: pathogenesis and cardiovascular risk. *Am J Therapeutics* 2006; 13: 248-260.
48. Vaughn G, Detels R. Protease inhibitors and cardiovascular disease: analysis of the Los Angeles County adult spectrum of disease. *AIDS Care* 2007; 19(4): 492-499.
49. D.A.D study group. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med* 2007; 356(17): 1723-1735.
50. Mehta NJ, Khan IA. HIV-associated coronary artery disease. *Angiology* 2003; 54: 269-275.
51. Tabib A, Leroux C, Mornex J, Loire R. Accelerated coronary atherosclerosis and arteriosclerosis in young immunodeficiency virus-positive patients. *Coronary Artery Disease* 2000; 11(1): 41-46.
52. Micheletti RG, Fishbein AF, Fishbein MC, Singer EJ. Coronary atherosclerotic lesions in human immunodeficiency virus-infected patients: a histopathological study. *Cardiovascular Pathology* 2009; 18: 28-36 (Epub 2008 Mar 4).
53. Rickerts V, Brodt H, Staszewski S, Stille W. Incidence of myocardial infarctions in HIV-infected patients between 1983 and 1998: the Frankfurt HIV-cohort study. *Eur J Med Res* 2000; 5: 329-333.
54. Klein D, Hurley LB, Quesenberry CP Jr, Sidney S. Do protease inhibitors increase the risk for coronary heart disease in patients with HIV1 infection? *J Acquir Immune Defic Syndr* 2002; 30: 471-477.
55. D.A.D. Study group. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med* 2003; 349(21): 1993-2003.
56. Hsue PY, Lo JC, Franklin A, *et al*. Progression of atherosclerosis as assessed by carotid intima-media thickness in patients with HIV infection. *Circulation* 2004; 109(13): 1603-1608.

57. Guiliano I, de Freitis S, De Sousa M, Bruno C. Subclinical atherosclerosis and cardiovascular risk factors in HIV-infected children: PERI study. *Coronary Artery Disease* 2008; 19(3): 167-172.
58. van Wyk JPH, de Koning EJP, Cabezas MC, *et al*. Functional and structural markers of atherosclerosis in human immunodeficiency virus-infected patients. *JACC* 2006; 47(6): 1117-1123.
59. Kingsley LA, Cuervo-Rojas J, Munoz A, *et al*. Subclinical coronary atherosclerosis, HIV infection and antiretroviral therapy: Multicenter AIDS Cohort Study. *AIDS* 2008; 22: 1589-1599.
60. Calza L, Manfredi R, Chiodo F. Statins and fibrates for the treatment of hyperlipidaemia in HIV-infected patients receiving HAART. *AIDS* 2003; 17: 851-859.
61. Boccara F, Teiger E, Cohen A. Stent implantation for acute left main coronary artery occlusion in an HIV-infected patient on protease inhibitors. *J Invasive Cardiol* 2002; 14(6): 343-346.
62. Spieker LE, Karadag B, Binggeli C, Corti R. Rapid progression of atherosclerotic coronary artery disease in patients with human immunodeficiency virus infection. *Heart Vessels* 2005; 20: 171-174.
63. Saporito F, Micari A, Raffa S, *et al*. Acute myocardial infarction and rescue percutaneous transluminal coronary angioplasty in a young HIV-infected patient. *J Clin Pract* 2005; 59: 376 -378.
64. Boccara F, Ederhy S, Janower S, *et al*. Clinical characteristics and mid-term prognosis of acute coronary syndrome in HIV-infected patients on antiretroviral therapy. *HIV Medicine* 2005; 6: 240-244.
65. Hsue PY, Giri K, Erickson S. Clinical features of acute coronary syndromes in patients with human immunodeficiency virus infection. *Circulation* 2004; 109: 316-319.
66. Matetzky S, Domingo M, Kar S, *et al*. Acute myocardial infarction in human immunodeficiency virus-infected patients. *Arch Intern Med* 2003; 163: 457-460.
67. Escaut L, Monsuez JJ, Chironi G, *et al*. Coronary artery disease in HIV infected patients. *Intensive Care Med* 2003; 29: 969-973.
68. Boccara F, Teiger E, Cohen A, *et al*. Percutaneous coronary intervention in HIV infected patients: immediate results and long term prognosis. *Heart* 2006; 92: 543-544.
69. Blyth DF, Buckels NJ, Sewsunker RR, *et al*. An experience with cardiopulmonary bypass in HIV-infected patients. *Cardiovasc J South Africa* 2006; 17(4): 178-185.
70. Trachiotis GD, Alexander EP, Benator D, Chargozloo F. Cardiac surgery in patients infected with the immunodeficiency virus. *Ann Thorac Surg* 2003; 76: 1114-1118.
71. Castillo JG, Adams DH, Rahmanian PB, Filsoufi F. Cardiovascular surgery in patients with HIV: Epidemiology, current indications and long-term outcomes. *Rev Esp Cardiol* 2008; 61(5): 480-486.
72. Boccara F, Cohen A, Di Angelantonio E, *et al*. Coronary artery bypass graft in HIV-infected patients: a multicenter case control study. *Curr HIV Res* 2008; 6(1): 59-64.
73. Font C, Miro O, Pedrol E, *et al*. Polyarteritis nodosa in human immunodeficiency virus infection: Report of four cases and review of the literature. *B J Rheum* 1996; 35: 796-799.
74. Sambatakou H, Tsiachris D, Stamouli S, *et al*. Systemic vasculitis with gastrointestinal involvement in a HIV-infected adult. *Am J Med Sc* 2008; 335(3): 237-238.
75. Golden MP, Hammer SM, Wanke CA, Albrecht MA. Cytomegalovirus vasculitis. Case reports and review of the literature. *Medicine* 1994; 73(5): 246-255.
76. Zaraa I, Maubec E, Valeyrie-Allanore L, *et al*. Haemolytic uraemic syndrome and acute mesenteric ischaemia caused by interferon-alpha-2b in the treatment of Kaposi's sarcoma in an AIDS patient. *Ann Dermatol Venereol* 2007; 134(1): 65-67.
77. Chahid T, Alfidja AI, Biard M, *et al*. Endovascular treatment of chronic mesenteric ischaemia: results in 14 patients. *Cardiovasc Interv Radiol* 2004; 27: 637-642.
78. Ghersin E, Motalvo BM. Arterial splenic calcifications in children with AIDS: two case reports. *Pediatr Radiol* 2002; 32: 387-389.
79. Ramanampamonjy RM, Ramarozatovo LS, Bonnet F, *et al*. Portal vein thrombosis in HIV infected patients: report of four cases. *Rev Med Interne* 2005; 26(7): 545-548.
80. Narayanan TS, Narawane NM, Phadke AY. Multiple abdominal venous thromboses in HIV-seropositive patient. *Indian J Gastroenterol* 1998; 17(3): 105-106.
81. Crum-Cianflone NF, Weekes J, Bavaro M. Thromboses among HIV-infected patients during the Highly Active Antiretroviral Therapy era. *AIDS Patient Care* 2008; 22(10): 771-778.
82. Carr A, Brown D, Cooper DA. Portal vein thrombosis in patient receiving Indinavir, a protease inhibitor. *AIDS* 1997; 112: 359.
83. Sagcan A, Tunc E, Keser G, *et al*. Spontaneous bilateral perirenal haematoma as a complication of polyarteritis nodosa in a patient with immunodeficiency virus infection. *Rheumatol Int* 2002; 21(6): 239-242.
84. Yonou H, Miyazato M, Sugaya K, *et al*. Simultaneous bilateral perirenal haematomas developing spontaneously in a patient with polyarteritis nodosa. *J Urol* 1999; 162: 483.