VASCULITIDES IN HIV-INFECTED CHILDREN

A Case Series & Literature Review

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in fulfilment of the requirements for the degree of

Master of Medicine in the branch of Paediatrics

Johannesburg, 2010
DECLARATION

I, Despina Demopoulos, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine (branch of Paediatrics) in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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Day of May, 2010
In memory of my father

Panayiotis Demopoulos

1949 - 2002
PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS STUDY

1. Poster presentation of patients at 25th International Congress of Pediatrics 2007; Athens, Greece


Pedmed October 2007
ABSTRACT

Medium and large vessel vasculopathy in HIV-infected patients is an uncommon but important cause of mortality and morbidity in both adult and paediatric patients. The estimated frequency in children from the current literature is 1-2%. The overall HIV prevalence among children 18 years of age and younger in South Africa is currently 2.9%.

This series reports on medium and large vessel vasculopathy in children with HIV. Six HIV infected children seen at three Johannesburg hospitals between 2000 -2006, are described, all presenting with complications arising from medium and/or large vessel involvement. Additional cases are reviewed from the literature. A description of the clinical presentation, radiological investigations, the possible aetiology, pathophysiology and management of these patients is presented.

The case series and literature review compares HIV vasculopathy and Takayasu’s arteritis. Both entities can present with multiple aneurysms and a diagnosis of tuberculosis, thus a possible link in the pathogenesis is explored.

Most patients with HIV vasculopathy present while severely immunosuppressed. However, some patients in the case series and literature review present despite adequate viral suppression, suggesting the possibility of an immune-reconstitution inflammatory syndrome in the pathogenesis of this vascular complication.

Medical management and in selected cases, surgery, has been used in the management of patients with HIV vasculopathy. The outcomes thus far are good.
ACKNOWLEDGEMENTS

1. Dr Willy Henderson, my supervisor, for his guidance, assistance and support at all times

2. Professor Alan D. Rothberg for his support and ideas on writing up the initial protocol

3. Dr Tim de Maayer, my second supervisor and friend, for his valuable input at short notice
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NOMENCLATURE

- ARV- Anti-Retroviral
- AZT- Zidovudine
- BP- blood pressure
- CD4%- percentage of CD4 lymphocytes
- CMV- Cytomegalovirus
- CNS- Central Nervous System
- CRP- C-reactive protein
- CT- computed tomography
- DNA- Deoxyribonucleic acid
- D4T- Stavudine
- HAART- Highly Active Anti- Retroviral Therapy
- HIV- Human Immunodeficiency Virus
- IgG- Immunoglobulin G
- IRIS-immune reconstitution inflammatory syndrome
- MR- magnetic resonance
- MRI- magnetic resonance imaging
- MTB- Mycobacterium tuberculosis
- PCR- Polymerase chain reaction
- TA- Takayasu’s arteritis
- TB- Tuberculosis
- VZV- Varicella Zoster virus
- 3TC- Lamivudine
1.0 INTRODUCTION

1.1 Background & review of pathophysiological mechanisms

Vasculitides in HIV-infected children is being increasingly recognised (incidence 1-2% per year).\(^1\) A broad range of vasculitides can be encountered, ranging from vasculitis resulting from specific infective agents to a non-specific vasculitis. Among the infective causes, cytomegalovirus and tuberculosis are probably the most common.\(^2\)

Small and medium sized vessels are more commonly involved. Aneurysm formation or occlusive disease of large elastic arteries (aorta, femoral, popliteal, carotid, and subclavian) is less frequently described.

The pathogenesis of the vasculopathy in HIV remains unclear. It might be associated with a known pathogen or triggering factor, or may occur in the absence of an obviously identifiable agent or aetio-pathogenesis. This means that almost all different types of aetiologies can be seen in HIV positive patients. Vasculitic processes in HIV-infected patients can be classified pathologically as 1) infective, 2) necrotising systemic diseases, 3) hypersensitive, 4) angiocentric immunoproliferative, 5) primary angiitis of the central nervous system, 6) large vessel vasculopathy and 7) miscellaneous.\(^2\)

Infective causes include CMV, TB and HIV. Necrotising systemic processes include polyarteritis nodosa-like lesions, and hypersensitivity examples include leucocytoclastic and eosinophilic vasculitis, and Henoch-Schonlein disease. Compared to small and medium vessel vasculopathy, large vessel vasculopathy presents as part of a leucocytoclastic vasculitis of the vasa vasora or periadventitial vessels, or is related to infection.\(^2\)
Theories regarding the pathogenesis include direct vascular endothelial infection with HIV, as evidenced by expression of viral proteins such as gp120 (envelope protein) or Tat (transactivator of viral transcription), or cytokines elaborated during the course of HIV infection of the immune system or secondary to opportunistic infections. Joshi et al. have suggested that elastases from repeated infections may injure the elastic lamina of vessels. Other authors describe increased secretion of vascular endothelial cell growth factor-A (VEGF-A) by T-lymphocytes in HIV-1–infected individuals that may induce vascular leakage and stimulate proliferation of vascular endothelial cells.

1.2 Vasculitides in HIV infected children

Vasculitis in an HIV positive child is an uncommon but important disease. In clinical studies, a 2.6% incidence of cerebrovascular disease has been documented in children with HIV. Martinez-Longoria et al. reviewed the literature up to 2004, and documented 24 cases of cerebral aneurysms in HIV-infected children. The majority of the patients presented with seizures, transient ischaemic events, hemiparesis or paraparesis, aphasia or motor deficits and fatal intracerebral haemorrhage. Conversely, large vessel (aorta, femorals, and carotids) vasculopathy is rarely described in children.

Medium and large vessel involvement can result in either multiple aneurysm formation or occlusive disease. These can be found in unusual sites such as the descending aorta, subclavian vessels, renal and internal carotid arteries.

Post mortem studies of HIV infected children showed an incidence of 64% with large vessel arteriopathy. The pathology focused on the vasa vasorum and consisted mainly of medial hypertrophy and chronic inflammation.
Other major pathologic findings identified in the affected arteries are intimal hyperplasia, fibrosis of the media, micro-calcifications, loss of muscularis, and destruction of the elastic internal layer, with the presence of infiltrates of mononuclear cells expressing HIV antigens on the endothelial surface of the affected vessels.

In previously reported cases, vascular disease in children was associated with severe immuno-suppression, particularly before the widespread use of highly active antiretroviral therapy (HAART).\textsuperscript{9}

Most of the reported cases had elevated viral loads and CD4+ cell counts below 15% of total lymphocytes. The optimal management of patients with HIV vasculopathy has not been well established. Medical management including HAART, in children has been used with good results.\textsuperscript{7}

**1.3 HIV vasculopathy and it’s association with tuberculosis & Takayasu’s arteritis**

Takayasu’s arteritis (TA) is a chronic, inflammatory vascular disease that primarily affects the aorta and its primary branches. The diagnosis of Takayasu’s arteritis can be confirmed by angiography, which often outlines a massively dilated aortic arch with aneurysmal dilatation and stenosis of various large vessels-carotids, subclavian, abdominal aorta, or, rarely in children, lesions of the coronary artery.\textsuperscript{10} In patients with HIV large vessel vasculopathy (aortic involvement), multiple aneurysms and a diagnosis of tuberculosis, a possible link between Takayasu’s arteritis and tuberculosis in the pathogenesis of large vessel vasculopathy needs to be investigated further.

The similarities in pathology to Takayasu’s arteritis, regarding large vessel involvement and multiple aneurysmal formation, have been noted previously.\textsuperscript{11}
This study will compare and contrast the presentation of tuberculosis in patients with Takayasu’s arteritis and HIV vasculopathy- the vessels involved, clinical presentation, histology, treatment and outcome.

1.4 Motivation for the study

Admissions of paediatric patients with large vessel disease are not frequently seen within the WITS Paediatric Academic Complex (including Chris Hani-Baragwanath Hospital, Charlotte Maxeke-Johannesburg Academic Hospital and Rahima Moosa Mother and Child Hospital). This series reviews the case records of six patients with medium and large vessel vasculopathy, seen within the complex between 2000 and 2006.

All patients presented with complications arising from medium and/or large vessel involvement. All cases were considered to have acquired HIV infection perinatally. Additional cases from the literature are reviewed.

The study was performed to look at the presentation, possible aetio-pathogenesis and prognosis of vasculopathy in HIV infected children. The study also aims to describe the role of the immune reconstitution inflammatory syndrome (IRIS) in the pathogenesis of this vascular complication. The study aims to include a comparison to Takayasu’s arteritis in the pathophysiology of HIV Vasculopathy.

Medical management, including the use of anti-retroviral treatment, of children with HIV vasculopathy has been used with good results, in some studies.
This study was also performed to review the available management of these affected children, as there are no guidelines or consensus as to the most effective strategies.

2.0 MATERIALS AND METHODS

2.1 Study sample

2.1.1 Geographic details

Children that presented within the WITS Paediatric Academic Complex were included in the case series. The complex consists of Charlotte Maxeke - Johannesburg Academic Hospital, Rahima Moosa Mother and Child Hospital and Chris Hani Baragwanath Hospital. Patients were managed by the HIV and Cardiology departments at these hospitals.

2.1.2 Age groups

The children in the case series were in the 1 to 12 year age group.

2.1.3 Sampling method

The study was a retrospective analysis of patient records. Convenience sampling was used. Children between the ages of 0 to 12 years presenting with HIV and medium/large vessel vasculopathy to the Wits Academic Complex between 2000 to 2006 were included in the case series.
The cardiology departments of the Wits Academic Complex and the HIV department at Rahima Moosa Mother and Child Hospital provided the data regarding the patient details.

Case series material and all information regarding patients (including special investigation results) were taken from patient hospital records.

There is a possibility that not all children with HIV and medium/large vessel vasculopathy were included in the study. Firstly, an extensive database search at the HIV, cardiology and renal departments’ at all three hospitals was not done. Secondly, screening for such patients is not done routinely. Thirdly, a few patients are possibly misdiagnosed due to the rarity of the disease entity. Fourthly, some patients may be asymptomatic.

2.1.4 Ethical considerations

Ethics clearance was obtained from the Wits Human Research Ethics Committee (Medical) (Protocol number M070341) (Appendix A).

2.2 Literature Review search strategy

A Pub med search was conducted. The following terms were used:

("HIV"[MeSH Terms] OR "HIV"[All Fields]) AND Vasculopathy [All Fields]) AND
("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields])

("HIV"[MeSH Terms] OR "HIV"[All Fields]) AND ("intracranial aneurysm"[MeSH Terms] OR ("intracranial"[All Fields] AND "aneurysm"[All Fields]) OR "Intracranial aneurysm"[All Fields])
There are 0 results out of 6602 records for: "HIV Vasculopathy in Title, Abstract or Keywords in Cochrane Database of Systematic Reviews"

There are 0 results out of 6602 records for: "HIV Vasculitides in Title, Abstract or Keywords in Cochrane Database of Systematic Reviews"

EMBASE was not used for the literature review as it is not available at our institution.
Human studies written in English were reviewed as this is the bulk of the articles in the literature. There were seven non-English articles found in the search—only one article related to neurological findings of HIV in paediatric patients. The other six articles referred to ocular complications, post herpetic vasculopathy, CMV encephalomyelitis, varicella zoster infection and portal hypertension with hepatitis C infection.

References from some of the major articles used were also consulted and included as references.
3.0 CASE SERIES

Patient 1 (SK)

Clinical presentation

A 12 year old male presented to Rahima Moosa Mother and Child Hospital on the 21\textsuperscript{st} September 2005 with an acute inability to walk and a right hemiparesis.

Past medical history

He previously had had numerous admissions for lower respiratory tract infections, lymphoid interstitial pneumonitis, molluscum contagiosum, herpes zoster and chorea. He had been treated for pulmonary tuberculosis 14 months prior to this presentation (July 2004).

He had been diagnosed as HIV infected at five years of age. He had been on various anti-retroviral regimens since the age of six. In 1999, he was started on Zidovudine(AZT) & Didanosine. In May 2004, he was changed to Stavudine, Lamivudine and Efavirenz, and in December 2004 changed to abacavir Lamivudine and Lopinavir/ritonavir. Failure of virologic suppression necessitated the changes.

Five months prior to this admission he presented with chorea. He had a CT Brain which showed a left caudate lobe enhancing lesion, with aneurysmal dilatation of the right internal carotid artery and its branches and an infarct of the head of the caudate nucleus (see figure 1.1).
Physical examination & Investigations

On physical examination he was disorientated and agitated. He was haemodynamically stable and had a right-sided hemiplegia. There were no signs of raised intracranial pressure. There was no chorea on neurological examination.

He had a white cell count of $6 \times 10^9$ per litre, haemoglobin of 13 grams per decilitre, platelets of $471 \times 10^9$ /l and a CRP < 1 mg/l. CD4% done on the 23rd August 2005 was 17%, with an absolute count of $593\text{cells/mm}^3$. The viral load was <400 copies/mm³.

An urgent CT Brain showed a right internal carotid artery aneurysm and a thrombosed anterior communicating artery aneurysm (see figure 1.2). An MRI revealed a dilated left and right middle cerebral artery. An echocardiogram showed a normal heart.

Management & Outcome

The patient was managed conservatively with rehabilitation. After fifteen months of follow up, he had improved clinically with no subsequent ischemic events and almost complete neurological recovery.
Figure 1.1

Post-contrast CT scan done 5 months prior to this admission, showing the left caudate lesion (arrow)
Figure 1.2
Follow up contrast CT Brain showing the right internal carotid artery aneurysm (arrow)
Patient 2 (DM)

Clinical Presentation

A 10 year old HIV positive male presented to one of our peripheral hospitals with right-sided weakness of the body. He was admitted to Rahima Moosa Mother and Child Hospital on the third of June 2006.

Past medical history

His medical history included several previous admissions for pneumonia. He was currently on treatment for pulmonary tuberculosis (unknown duration as caregiver not present) as well as HAART (AZT, 3TC, Efavirenz) which had been initiated 3 months prior to his presentation.

Physical examination & Investigations

On physical examination he was pale and mildly confused. He was haemodynamically stable (BP 113/63) and had a right hemiparesis with a right upper motor neuron VII nerve palsy.

Haemoglobin was 2 grams per decilitre and a thrombotic work up, and tuberculin skin tests were negative. Lumbar puncture was normal (0 polymorphs, 0 lymphocytes, 8 red blood cells, protein 0.41 g/l, glucose 3.4 mmol/l, and chloride 121 mEq/l). His CD4% was not available.

A contrast CT Brain showed white matter oedema of the left hemisphere, with associated ventriculomegaly. There was no evidence of arterial or venous thrombosis. An echocardiogram to exclude an embolic cause was normal.

A CT reconstruction Angiogram showed a left internal carotid artery occlusion (see figure 2)
Management & Outcome

The patient was transfused and treated conservatively. He received rehabilitation in the ward and his power and tone improved. He was transferred back to his referring hospital for further care. HAART was continued and follow up was to be done at the referring hospital.

Figure 2

CT reconstruction Angiogram with left internal carotid artery occlusion. ECA= External carotid artery CCA= Common carotid artery IJV= Internal Jugular Vein
Patient 3 (KM)

Clinical Presentation

A six year old HIV-infected female presented with a one day history of vomiting. She was admitted on the 28th November 2006 to Rahima Moosa Mother and Child Hospital.

Past medical history

She had had no previous admissions. HAART had been initiated six months previously (D4T, 3TC, Efavirenz) as she was severely immunosuppressed with a CD4 count of 4.98% (absolute count of 94 cells/mm$^3$), and a viral load of 28 copies/mm$^3$.

Treatment for pulmonary tuberculosis was completed two weeks prior to her presentation.

Physical examination & Investigations

On physical examination she was mildly dehydrated, and had oral candidiasis. Her blood pressure was elevated at 149/112 mmHg but she had no neurological signs initially. The following day, however, she presented with an acute left hemiparesis thought to be due to a hypertensive encephalopathy (BP 170/122mmHg right arm supine). She was started on anti-hypertensive medication and her BP was controlled after a few days.

Her white cell count was $11.5 \times 10^9$ per litre, haemoglobin 9.7 g/dl and platelets 435 $\times 10^9$. Lactate was 6.2 mmol/l (repeat lactate 4.2mmol/l), CRP 5 mg/l and her lumbar puncture showed 3 polymorphs, 0 lymphocytes, 70 red blood cells, protein 0.28 g/l, glucose 4.3 mmol/l, and chloride 121 mEq/l with a negative culture. The INR was 0.97 and blood cultures were negative.
A contrast CT brain showed aneurysms of the right internal carotid artery, the right vertebral as well as the basilar artery. On ultrasound of the abdomen, both kidneys were enlarged. The left ventricle was myopathic on echocardiogram with a reduced ejection fraction of 30%. In addition, an apical thrombus was noted in the left ventricle (figure 3).

**Management & Outcome**

Anti-cardiac failure and anti-coagulation therapy was started, and her left ventricular function normalised after three to six months. She had a residual left sided weakness and evidence of neuro-cognitive impairment at six month follow up. Follow up CT scan of the brain in July 2009 showed a calcified aneurysm (figure 3.2).

**Figure 3.1**

Apical 2-chamber echocardiogram showing a dilated LV with an apical thrombus (arrow).
Figure 3.2 Follow up contrast CT Brain, showing the aneurysm, with areas of calcification
Patient 4 (CW)

Clinical Presentation

This seven year old male presented with a two day history of severe weakness on the right side, with inability to walk, irritability, and drowsiness. He had been limping for two weeks. He was admitted on the 26th December 1999 to Rahima Moosa Mother and child Hospital.

Past medical history

He was diagnosed with HIV at age five after numerous admissions. He had also been treated for pulmonary tuberculosis at age five years (April 1997) based on a combination of a positive tuberculin skin test, radiological findings and a positive maternal TB contact. Unfortunately he presented at a time before anti-retroviral treatment was made widely available in public hospitals. Anti-retroviral treatment became available in public hospitals in April 2004. His CD4% count was also unavailable.

In addition, his other medical diagnoses included cor pulmonale, lymphoid interstitial pneumonitis and herpes zoster. In April 1998, there was a documented episode of bacterial meningitis when he presented with right-sided focal seizures and a right hemiparesis which subsequently resolved. A CT scan of the brain was reported as normal at the time. TB treatment was re-commenced (although the TB Bactec was negative, but there was a suspicion of TB Meningitis as the lumbar puncture showed 325 polymorphs, 290 lymphocytes, 3520 red blood cells, protein >5 g/l, glucose 3.5 mmol/l, and chloride 101 mEq/l with an ADA of 1.2). In January 1999, he presented with a left hemiparesis and a cataract and in April 1999, with a right hemiparesis which subsequently resolved.
Physical examination & Investigations

On physical examination, this ill child had a decreased level of consciousness (Glasgow Coma scale 10/15). There were meningeal signs, associated with a right hemiparesis and right upper motor neurone VII nerve palsy.

Contrast CT scan of the brain showed aneurysmal dilatation of the vessels of the Circle of Willis, with left hypothalamic calcifications. Cerebro-spinal fluid was normal except for a mildly elevated protein concentration (Protein 0.73 g/l, Glucose 2.9 mmol/l, Chloride 131mEq/l, polymorphs 0, lymphocytes 1, erythrocytes 0; serum glucose 6.6 mmol/l).

Management & Outcome

He was transfused (haemoglobin was 5.7 g/dl) with packed cells and intravenous cefotaxime and acyclovir were commenced. His TB treatment (Re-treatment started a few months earlier) was continued. Investigation for TB was not performed as he was already on TB treatment. Unfortunately, he did not improve and demised 20 days after admission.

A pre-mortem repeat CT scan of the brain revealed a right subdural haemorrhage with massive midline shift. A post mortem was performed and macroscopic changes included vascular ectasia of the posterior communicating arteries in the circle of Willis (figure 4), aseptic meningitis and a small pontine infarct. Histo-pathological findings of the vessels included medial fibrosis of the large vessels of the Circle of Willis, destruction of the internal elastic lamina, and intimal hyperplasia.
Figure 4

Post mortem specimen showing aneurysms of posterior communicating arteries (arrows) in the circle of Willis.
Patient 5 (TN)

Clinical Presentation

This three year old male presented with a chronic cough, recurrent scabies lesions, fever and loss of weight. He was admitted on the 11\textsuperscript{th} October 2002 to Chris Hani Baragwanath Hospital.

Past medical history

He had had no previous admissions and no known TB contacts. However, his father had died 6 months previously with symptoms of severe loss of weight and coughing, the cause of which was unknown.

Physical examination & Investigations

On physical examination, the child was wasted with generalised lymphadenopathy, a hepatomegaly, pallor, bilateral non-tender parotidomegaly, clubbing of the digits and infection of the skin with scabies. He had mild systemic hypertension with a BP of 135/70mmHg. In addition, there was cardiomegaly with right ventricular failure and pulmonary hypertension. Respiratory and central nervous system examination were normal.

The enzyme-linked immunosorbent assay was positive for HIV and a mantoux skin test for tuberculosis was positive, with a diameter measuring 20 millimetres.

His white cell count was $12.8 \times 10^9/l$, haemoglobin 7.8 g/dl and platelets $553 \times 10^9/l$. His CD\textsubscript{4} count was 7.70% (Absolute count of 325 cells/mm\textsuperscript{3}).

The chest X-Ray showed cardiomegaly consistent with the clinical findings and, in addition, showed bilateral reticulonodular infiltrates, consistent with a possible diagnosis of lymphoid interstitial pneumonitis.
A transthoracic echocardiography revealed biventricular dilatation, with a decreased left ventricular function, with an ejection fraction of 35%. A dilated brachiocephalic trunk and an eccentric suprarenal aneurysm of the descending aorta with an intraluminal thrombus were noted. An additional ultrasonic examination by the radiologists, showed a small right kidney (measured 6.3 cm) compared to the left kidney (measured 8.1 cm).

Angiography of the aorta confirmed the echocardiographic findings (figure 5).

In addition, dilation of the origin of the left coronary artery, and an extensive stenosis of the right renal artery were also seen, which explained the smaller right kidney seen on ultrasound.

Management & Outcomes

Treatment for hypertension, for tuberculosis as well as for heart failure, was commenced. Oral prednisone was prescribed for a presumed arteritis of the large arteries. At six weeks follow up, the patient had improved markedly. He was no longer in heart failure and his blood pressure had settled to 100/60mmHg.

He was re-admitted nine months later with a left hemiparesis. His blood pressure was 100/70mmHg and he had no signs of raised intracranial pressure. A CT scan of the brain showed a non-haemorrhagic right anterior and middle cerebral infarct. On repeat echocardiogram, there were no intra-cardiac thrombi or vegetations and the ejection fraction had normalised to 73%.

A carotid Doppler revealed an organising thrombus of the left brachiocephalic trunk. Aspirin was started and he received rehabilitation. He was discharged 13 days later.

At follow-up his left hemiparesis was resolving. His blood pressure was controlled as was his heart failure. Unfortunately he had not been started on HAART as there were social issues that could not be immediately resolved.
Aortogram showing aneurysmal dilatation of the arch at the junction of the transverse arch and descending aorta (black arrow), and the brachiocephalic trunk (white arrow)
Patient 6 (JN)

Clinical Presentation

This 16 month old HIV positive female presented with acute gangrene of the right hand and third and fourth digits of the left hand. She was admitted on the 7th October 2002 to Chris Hani Baragwanath Hospital.

Past medical history

She had multiple previous admissions for gastro-enteritis, TB, bacterial pneumonia and scabies. She was diagnosed with TB in March 2002 due to a positive tuberculin skin test. Poor compliance meant that she never completed a course of TB treatment.

Physical examination & Investigations

On physical examination she was undernourished with significant lymphadenopathy and hepatosplenomegaly. Both brachial pulses were absent. Femoral pulses were palpable but were of poorer volume on the left side. Unfortunately, no blood pressure recordings were documented. There was rapid progression of the dry gangrene up both forearms up to the level of the elbows over the next ten days, during which time the toes of the left foot also became gangrenous (figure 6.1).

Laboratory studies showed a white cell count of $26 \times 10^9/l$, haemoglobin 7 g/dl and platelet count of $246 \times 10^9/l$. Her CD4 count of 451 cells/mm$^3$ was decreased indicating severe immunosuppression. There was no documentation of arterial blood gases having been taken that could have possibly resulted in arterial trauma.

An echocardiogram showed mild left ventricular dysfunction with an ejection fraction of 54%. There was no visible intracardiac thrombosis. The left coronary artery was dilated, and the descending aorta was irregular below the level of the diaphragm. An ascending aortogram confirmed dilated
coronary arteries as well as an abrupt discontinuation of both subclavian arteries (indicating subclavian artery occlusion). In the abdominal aortogram, there was irregularity of the silhouette of the descending aorta below the coeliac plexus (indicating possible aneurysmal dilatations and stenosis). In addition, the superior mesenteric artery was dilated with an irregular silhouette; both renal arteries were stenosed and aneurysmal (figure 6.2)

Management & Outcome

The subsequent fate of the patient is not known as the family requested an immediate discharge, and there was no follow up.
Figure 6.1

Gangrene of both arms
Figure 6.2

Abdominal aortogram showing irregularity of the descending aorta below the coeliac trunk. The superior mesenteric artery is dilated & irregular; both renal arteries are stenosed and aneurysmal (arrows)
## Table 1 SUMMARY OF CASE SERIES OF HIV VASCULOPATHY IN CHILDREN

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<td>Systemic hypertension</td>
<td>Right hemiparesis</td>
<td>Systemic hypertension</td>
<td>Gangrene both arms</td>
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<td></td>
<td></td>
<td></td>
<td>Left hemiparesis</td>
<td></td>
<td>Left hemiparesis</td>
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<tr>
<td>CD4 Absolute Number (cells/mm$^3$) (CD4 %) Viral load (copies/mm$^3$)</td>
<td>593 (17%)</td>
<td>Unknown</td>
<td>373 (15.1%)</td>
<td>Unknown</td>
<td>325</td>
<td>451</td>
</tr>
<tr>
<td>Duration of Anti-retroviral therapy</td>
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<td>3 months</td>
<td>6 months</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Associated conditions</td>
<td>Pulmonary Tuberculosis ; Lymphocytic Interstitial pneumonitis ; Molluscum contagiosum ; Herpes zoster (past)</td>
<td>Pulmonary Tuberculosis (current)</td>
<td>Pulmonary Tuberculosis (past) ; Cardiomyopathy with LV thrombus (current)</td>
<td>Pulmonary Tuberculosis (present) ; Lymphocytic Interstitial pneumonitis (past) ; Cor pulmonale ; Herpes zoster Cataract (left) (past)</td>
<td>Pulmonary Tuberculosis ; Lymphocytic Interstitial pneumonitis (present)</td>
<td>Pulmonary Tuberculosis (past)</td>
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Irregularity of
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<tr>
<th>CT/MRI / Angiography Findings</th>
<th>Right internal carotid artery aneurysm</th>
<th>Left internal carotid artery occlusion</th>
<th>Right internal carotid, right vertebral and basilar artery aneurysms</th>
<th>Aneurysms of vessels of the Circle of Willis</th>
<th>Right frontoparietal infarct</th>
<th>Outcome</th>
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<tr>
<td></td>
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<td></td>
<td>descendent aorta</td>
<td>Almost complete neurological recovery</td>
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<td></td>
<td>Dilated superior mesenteric artery</td>
<td>Improved neurologic function</td>
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<td></td>
<td>Renal arteries stenosed and aneurysmal</td>
<td>Residual left sided weakness Neuro-cognitive impairment</td>
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<tr>
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<td>Unknown</td>
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<td></td>
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<td></td>
<td></td>
<td>Medial fibrosis, destruction of internal elastic lamina and intimal hyperplasia of branches of circle of Willis; Vascular ectasia with aneurysms</td>
<td>Medial fibrosis, destruction of internal elastic lamina and intimal hyperplasia of branches of circle of Willis; Vascular ectasia with aneurysms</td>
</tr>
</tbody>
</table>
4.0 LITERATURE REVIEW AND DISCUSSION

4.1 PREVALENCE

The overall HIV prevalence among children 18 years of age and younger in South Africa is currently 2.9%.\(^1\) Vasculitides in HIV-infected children is being increasingly recognised (frequency 1-2%).\(^1\) Medium and large vessel involvement can result in either multiple aneurysm formation or occlusive disease. These can be found in unusual sites such as the descending aorta, subclavian vessels, renal and internal carotid arteries.

Aneurysms occurring in association with HIV were first reported in three patients from Zimbabwe and one from the USA in 1989.\(^1\)\(^3\) Since then there have been isolated case reports with a few case series on aneurysms in HIV infected patients. In these reports, the documented aneurysms have involved mostly the extracranial arteries, including the common carotid and its branches, the subclavian arteries, aorta, femoral artery and its branches, and the popliteal arteries.\(^1\)\(^4\)-\(^1\)\(^6\)

An extensive study on extracranial aneurysms in HIV positive patients, reported from KwaZulu-Natal, South Africa, found that the patients were young, with no risk factors for degenerative arterial disease, multiple vessel involvement was common and atypical sites were involved.\(^1\)\(^6\) The histology showed fragmentation with loss of the internal elastic lamina, medial and adventitial fibrosis with chronic inflammation, leukocytoclastic vasculitis and proliferation of slit-like vascular channels in the adventitia.\(^2\)\(^,\)\(^1\)\(^4\)\(^,\)\(^1\)\(^7\)
Childhood HIV-associated intracranial fusiform\* aneurysmal vasculopathy has been reported in 2.6% of children with HIV.\(^6\) There are over 32 case reports of HIV-positive children, most of whom were severely immunocompromised in the era before HAART, with fusiform aneurysms on arteries of the circle of Willis, resulting in ischaemic and haemorrhagic strokes, and leading to death within six months.\(^7,18-20\) Paediatric autopsies revealed aneurysmal dilatation confined to the large arteries of the circle of Willis, sparing the leptomeningeal and intraparenchymal arteries.

Twelve adult cases of intracranial fusiform vasculopathy have been described.\(^21\) These patients tend to have CD4 counts below 200 cells/mm\(^3\) and high HIV viral loads. Radiographic findings include characteristic diffuse fusiform aneurysms often with haemorrhage or infarct. Clinical presentations among adults include confusion, cognitive deficits, dysarthria, and hemiparesis.

In the paediatric literature, children can present with seizures, hemiparesis, headache, movement disorders, recurrent CNS infections or asymptotically where lesions are picked up incidentally on screening.\(^22-24\)

### 4.2 AETIOLOGY

The aetiology of HIV-associated intracranial vasculopathy remains unclear. Human immunodeficiency virus (HIV), along with other pathogens, may play a role but the exact mechanism of vessel damage remains undefined. Reported causes of infective intracerebral aneurysms in patients with HIV include salmonella, *Mycobacterium tuberculosis* (MTB), meningo-vascular syphilis, cytomegalovirus (CMV), and others.\(^2,25\) However, in many reported

\* Fusiform aneurysm: a localized dilation of an artery in which the entire circumference of the vessel is distended. The result is an elongated, tubular, or spindle-like swelling.
cases, an infective cause other than HIV is not found. Mycotic aneurysms from bacterial or fungal organisms are usually fusiform and located in distal arterial branches.\textsuperscript{21}

Some authors have suggested a role for MTB or atypical mycobacterial infection in causing these intracranial aneurysms, because mycobacteria are a known cause of infective vasculitides in patients with HIV, and several paediatric cases had concurrent mycobacterial infection.\textsuperscript{21} Intracranial tuberculous aneurysm rupture has been described in a single case report of a patient with tuberculous meningitis.\textsuperscript{26}

Of 12 adult cases with diffuse cerebral vasculopathy,\textsuperscript{21} two were on therapy for pulmonary TB at the time of presentation; five patients had CSF examined for acid-fast bacillus or adenosine deaminase, and all were negative, although one was still subsequently treated for presumed tuberculous meningitis; and only one patient had an atypical mycobacterial infection near the time of presentation.

CMV vasculitis of the CNS has been documented in 2\%–13\% of autopsy specimens from patients with AIDS.\textsuperscript{27} Vasculitis may involve meningeal vessels as well as extradural vessels of the brain and spinal cord. Koeppen et al. described an adult male who developed blindness, deafness, and paraplegia after intrathecal methotrexate for presumed CNS lymphoma.\textsuperscript{28} Autopsy revealed chorio-retinitis, arteritis of the ophthalmic artery with infarcted optic nerve, occlusive arteritis with multiple infarcts of the brain and spinal cord, and small and medium vessel vasculitis in the brain and thoracic cord. Electron microscopy of the brain and retina revealed abundant intranuclear inclusion bodies compatible with CMV. Single or multiple intracranial aneurysms, however, have not been reported in CMV infection.

Productive varicella zoster virus (VZV) infection of cerebral arteries is another possible cause of cerebral fusiform vasculopathy in patients with HIV. VZV infects large and small cerebral arteries,
causing aneurysms and necrotizing angiitis. Pathology of affected larger cerebral arteries has revealed a necrotizing arteritis or intimal proliferation occluding the lumina with stenosis or thrombosis, often with positive VZV-immunostaining. Unifocal, large-vessel infarction from VZV occurs in elderly, immuno-competent persons with recent zoster, and is likely due to transaxonal migration of VZV from trigeminal nerve afferent fibers to vessels of the anterior cerebral circulation. Multifocal VZV vasculopathy affects branches of large or small cerebral arteries in immunocompromised patients. Saraya et al. described an HIV-positive adult with multiple intracranial aneurysms along smaller peripheral arteries, suggesting viral spread via cerebral arteries, and not the trigeminal nerve.

Nagel et al. described 30 patients with VZV CNS vasculopathy, five of whom were HIV-positive and 37% of whom lacked a history of varicella zoster infection or rash. The absence of CSF pleocytosis was noted in 33% of patients. Anti-VZV IgG antibody in the CSF was a more sensitive marker of cerebral VZV infection than CSF VZV DNA (93% vs. 30%). Others have also shown that a reduced ratio of the concentration of anti-VZV IgG in serum to that in CSF as compared with the ratios of total IgG and albumin supports the diagnosis of active VZV CNS infection.

Several cases of CNS vasculopathy in HIV-infected children cite VZV as a possible causative agent. Fulmer et al. report a child with AIDS and fusiform dilatation of the anterior and posterior cerebral arteries with positive immunohistochemical staining against VZV of the dilated vessels. In a series of 13 paediatric cases of cerebral aneurysmal arteriopathy, four had a history of infection and two had elevated serum VZV antibody titres, but none had VZV infection confirmed in the CNS; two postmortem CNS examinations with VZV immunostaining were both negative.
Of the 12 adult cases, CSF VZV DNA PCR was negative in three patients and not reported in the remainder. A fourth patient had an elevated VZV serum antibody level and a positive serum VZV PCR, but no reported CSF studies; this patient had clinical and radiographic improvement that authors attributed to high-dose intravenous acyclovir and steroids. VZV immunostaining was not performed on the single adult case that went to autopsy.

The human immunodeficiency virus (HIV) itself has been implicated as the cause of intracranial vasculopathy. One theory proposes that HIV or opportunistic infection causes immune activation with cytokine and growth factor production, causing vascular remodelling. Others postulate that HIV directly invades and damages cerebrovascular endothelium. With only two exceptions, all reported adult and paediatric cases, including patients on ARV, had highly elevated HIV viral loads upon presentation with aneurysmal disease. However, in only one paediatric case were HIV sequences detected by PCR in an affected intra-cerebral artery. Kure et al. described a paediatric case with positive anti-gp41 antibody staining of cells in the organizing thrombi and the thickened intima of the involved artery from the circle of Willis, and suggested that positive-staining cells in the intima were not endothelial cells, but rather were derived from haematogenous cells involved in ongoing thrombi. The single published adult autopsy reported a negative p24 antigen staining of vessel sections.

If an opportunistic infection is the aetiologic agent for the intracranial vasculopathy, one concern is that initiating ARV would prompt the immune reconstitution inflammatory syndrome (IRIS) and possibly worsen the underlying vasculopathy. Bonkowsky et al. described a 12-year-old boy with perinatally acquired HIV infection and poor compliance on numerous ARV regimens who, six months after switching to a new ARV regimen with excellent immunologic recovery and suppression of his viral load, developed acute neurologic symptoms with diffuse fusiform aneurysms in large cerebral vessels and acute infarction. Patient 1 and Patient 3 from our case
series also developed neurological symptoms 3 to 6 months after HAART initiation. Thus AIDS-associated cerebral aneurysms may be a complication of chronic vascular endothelial infection that may be exacerbated by the immune response.35

One adult case report documents a patient who suffered a basal ganglion haemorrhage several weeks after initiating ARV and reducing her decadron dosing (initially started for a possible autoimmune vasculitis); she was retreated with high-dose methylprednisolone and then transitioned to a 12-month prednisone taper.21

The possibility of an IRIS needs to be considered in these four patients (Bonkowsky’s patient, our patient 1 and 3 and the adult patient mentioned above).

Other cases in the literature, including our other patients, tend to be significantly immunosuppressed.35 Adults with HIV-associated intracranial aneurysmal vasculopathy had CD4 counts below 200 cells/mm³ and viral loads greater than 100,000 copies/ml. They present with significant neurologic dysfunction and characteristic radiographic findings of diffuse cerebral fusiform aneurysms.

4.3 TAKAYASU’S ARTERITIS AND HIV VASCULOPATHY

Previous studies suggest that similarities exist between Takayasu’s arteritis (TA) and HIV large vessel vasculopathy.11 Kalungi et al. in Uganda and Shingadia et al. in Chicago, Illinois each described a patient with HIV and Takayasu’s arteritis.41,42

The cause of TA remains unknown, although histopathology and immunohistochemistry of biopsy and autopsy samples from adults with TA suggest a primarily T-cell–mediated mechanism.43 Pathologically TA lesions consist of granulomatous changes progressing from the vascular adventitia to the media. A proposed hypothesis for the pathogenesis of granulomatous
Vasculitis suggests that antigens deposited in vascular walls activate CD4+ T cells, inducing the release of cytokines, and monocyte chemotaxis. These monocytes are transformed into macrophages that mediate endothelial damage and result in granuloma formation in the vessel walls.44

The diagnosis of TA is based on the distribution of involvement, primarily the aorta and its branches, and the young age of patients, typically less than 40 years. Signs and symptoms include hypertension, cardiomegaly, elevated ESR, fever, fatigue, palpitations, vomiting, subcutaneous nodules, abdominal pain, arthralgia, claudication, weight loss, and chest pain.

Once TA is suspected, angiography has been the standard method used for diagnosis. The size of the vessels involved and the patchy nature of the vascular inflammation make biopsies impractical. In recent years, CT and MR angiograms have proven to be as useful as traditional angiograms and are far less invasive. MRI has the added advantage of revealing evidence of ongoing vessel wall inflammation. This is useful because of the need to suppress the vasculitis completely to prevent disease progression. None of the patients in the case series had been given the diagnosis of TA but patient 5 had been put on oral prednisone for a suspected vasculitis. Steroids and the typical immunosuppressive agents used in other vasculitides (including cyclophosphamide, methotrexate, and azathioprine) have shown variable efficacy in TA. A recent report in adults with TA from the Cleveland Clinic documented a high response rate to TNF-inhibitors.43 Before starting such treatment it is important to test patients for tuberculosis, because aortitis is associated with mycobacterial infections, especially in less developed countries.43

Although TA is common in the parts of the world with high incidences of tuberculosis, there are exceptions such as Japan. 44
Hahn et al. showed that 90% of patients presenting to two South African Nephrology units with TA had a strongly positive Mantoux test. Toma reported a 70% incidence of positive tuberculin reactions and Reddy reported 60% of their patients had a positive Mantoux or previous history of tuberculosis.

Gulati however commented that there is an increased skin hypersensitivity to the purified protein derivative (PPD) in patients with TA and this is not attributable to past or current infection with *M. tuberculosis*. The precise association of TA with tuberculosis is unclear, and the condition of patients with TA does not improve following anti-tuberculous treatment.

Patients with Takayasu’s arteritis can present with systemic symptoms including fever, night sweats, fatigue, weight loss, myalgia, skin rash, headaches, syncope, congestive heart failure, angina and hypertension. Complications of the resultant ischaemia include stroke, transient ischaemic attack, visual disturbances, abdominal pain and claudication. These are similar to the clinical presentation of patients with HIV large vessel vasculopathy who present with multiple aneurysms and occlusions. Both entities have had patients with a co-morbid diagnosis of tuberculosis. This occurrence suggests a possible link between Takayasu’s arteritis and tuberculosis in the pathogenesis of large vessel vasculopathy.

Currently, in the world literature, less than 10 patients have been reported to have a co-diagnosis of both Takayasu’s arteritis and HIV. This is surprising, particularly in countries with large burdens of HIV, such as South Africa, where one would expect to see many more cases. Currently there are only four children with a co-diagnosis of HIV and Takayasu’s arteritis documented in the Paediatric Nephrology clinic databases in the Wits University complex. Perhaps the immune suppression associated with HIV precludes the development of TA, which is caused by an exuberant immune response. As the clinical presentation is similar between the
two entities we cannot always differentiate between HIV vasculopathy and Takayasu’s arteritis. Perhaps some of the patients in the clinical series actually had the diagnosis of TA and patients with HIV and TA in the literature search actually only had HIV vasculopathy and not TA. Further research is required to define if there is a connection between HIV vasculopathy and TA.

4.4 MANAGEMENT

Despite over 30 case reports in the paediatric literature and 12 reported adult cases, optimal therapy for HIV Vasculopathy remains undefined. There is some suggestion that initiating ARV or optimising a previous ARV regimen will stabilise or reverse intracranial aneurysmal vasculopathy.

In the adult literature, survival to discharge has been documented in two of three patients who were already receiving HAART at presentation with vasculopathy; in three of four patients who started HAART after presentation with vasculopathy; and in one of five patients who never received HAART.\(^9,13,18,37-39\)

Martinez-Longoria et al. described a child whose intracerebral aneurysm underwent complete radiographic resolution on an optimised ARV regimen, but her initial presentation was atypical in that she initially had only a single aneurysm as well as angiographic evidence of arteritis.\(^7\)

Elfenbein et al. described a child with progression of neurologic symptoms despite immune recovery with HAART,\(^49\) and Mazzoni et al. described a paediatric case with clinical improvement and radiographic stabilisation of vasculopathy after optimisation of ARV therapy.\(^19\) Three of our patients improved neurologically with HAART and rehabilitation.

Based on a literature review by Goldstein et al., initiation of ARVs may be a reasonable approach for treatment of fusiform vasculopathy in patients infected with HIV.\(^21\) There is no evidence that
supports one ARV regimen over another, but the following factors should be considered when selecting a regimen: the HIV genotypic and/or phenotypic resistance profile in the patient, the toxicity profile and the tolerability of an ARV regimen, and the ability of an ARV regimen to penetrate the blood-brain barrier. Some ARVs that penetrate the CNS include zidovudine, lopinavir/ritonavir, and nevirapine. While it is unclear whether CNS drug penetration is necessary for the patient population; the CNS has been documented to be a reservoir site for HIV replication.

Steroids have an undefined role in treating this HIV associated vasculopathy and in preventing IRIS. Paediatric cases of HIV-associated intracranial fusiform vasculopathy have been treated with ARV and aspirin, but not with steroids. Of the five adult patients who survived at least one month after hospital discharge, all received ARV therapy and the majority (60%) received both steroids and ARV therapy. Of the three adult patients who received steroid therapy following vasculopathy diagnosis, one received an unspecified dose and duration of corticosteroids; one received prednisolone 1000 mg for four days; and one received dexamethasone and then, after repeat intracranial haemorrhage, methylprednisolone and a prolonged prednisone taper. All three of these patients survived (3 months, 4 months, and 18 months, respectively). Of note, each also began an ARV regimen around the time of steroid initiation. Defining the mechanism of benefit of steroids is problematic because the mechanism of vasculopathy is unknown.

As autopsy studies did not reveal a vasculitis, authors like Goldstein et al. do not feel that high-dose steroids for prolonged duration are indicated, as for CNS vasculitis. However, an abbreviated course of steroids may be a consideration during the initiation of the ARV therapy for the prevention of IRIS. They suggest a steroid regimen which includes prednisone started at 1 mg/kg given as a single dose followed by a taper and discontinuation of the drug over a three
month period. Despite these limited data, in patients with HIV and the characteristic radiographic findings of diffuse cerebral vasculopathy, they recommend treating any active infection, then initiating ARV and steroids in a timely manner. Special attention should be given to the possible development of IRIS.

A South African study of 226 patients with HIV vasculopathy (ages 4-53 years) states that surgical therapy for aneurysms is worthwhile in the short term. The study involved mainly extracranial sites. Records were culled from a prospectively maintained data base on the Vascular Unit at Inkosi Albert Luthuli Hospital, Durban, South Africa between January 2005 and June 2009. Of the patients presenting with aneurysms, the commonest sites were the superficial femoral artery (40%) and carotid artery (25%). Eighty-two patients had standard operative repair and eight had stent grafts. Twenty nine patients were excluded due to advanced disease. Within 30 days of operation the mortality was 9%, with 5% developing graft sepsis and 11% pulmonary complications.

Of 115 patients with occlusive disease, there were two distinct groups. Fifty-one had no previous claudication and had acute thrombosis; no thrombophilia could be demonstrated. Sixty four had premature atherosclerotic disease. The majority presented with critical ischaemia. In the acute thrombosis group 15 (29%) had primary amputation, limb salvage was achieved in 13 (36%) and four died (11%). In the chronic occlusive group 30 (47%) had primary amputation, of 25 submitted to surgery limb salvage was achieved in 17 (68%).
4.5 STUDY LIMITATIONS

Limitations include the small sample of patients in the case series and the involvement of only one centre (Wits complex). Little inference can be made with regard to treatment as this was an observational study, there were no controls to identify risk factors, aetiology and management strategies. The study was retrospective which relies on information from other clinicians. HIV Vasculopathy in children is under diagnosed which limits the number of patients included in the series.

The literature review was not exhaustive, due to the lack of access to EMBASE, and the exclusion of non-English articles.

4.6 RECOMMENDATIONS FOR FUTURE RESEARCH

As this is a rare disease entity, multicenter, multinational randomised control studies with long term follow up are necessary.

In terms of the pathogenesis, researchers need to look for any infection (including CMV, VZV, Herpes, TB) and autopsy studies or case control studies (as it is a rare disease) need to be done looking for risk factors.

The immune status of each patient needs to be well documented. Clinicians need to be aware of IRIS and screen patients with neurological signs.
Long term follow-up after surgical or medical therapy needs to be well documented to assist with prognosis.

### 5.0 CONCLUSION

Vasculopathy in an HIV-positive child is an uncommon but important disease. A large-vessel (aorta and femoral and carotid arteries) vasculopathy is rarely described in children with HIV.

The incidence of cerebrovascular disease has been reported as 2.6% in children with HIV.\(^6\)

Medium- and large-vessel involvement can result in either multiple aneurysm formation or occlusive disease, as seen in our patients. Unusual sites such as the descending aorta, subclavian vessels, and renal and internal carotid arteries can be affected.

Previously reported cases of vascular disease in children were associated with severe immunosuppression.\(^9\) These cases were reported before the widespread use of highly active antiretroviral therapy (HAART) but, in our series, patients 1, 2 and 3 had been on a standard HAART regimen for an average of six months before presenting. Patients 1 and 3 were virally suppressed. The immune-reconstitution inflammatory syndrome (IRIS) could be implicated in the pathogenesis of their vascular complications.\(^53\) IRIS occurs within a few weeks to months after the start of HAART; patients most often present with clinical manifestations while the number of CD4 lymphocytes is increasing and the HIV viral load decreasing, as was probably the case in these three patients.

All our patients had been treated for pulmonary tuberculosis on the basis of clinical suspicion and investigations. The similarities in pathology to Takayasu’s arteritis (aetiology unknown) with regard to large-vessel involvement and multiple aneurysm formation have been noted previously.\(^11\)
The precise mechanisms of vascular injury in HIV require further study. An infectious cause needs to be excluded. Children with HIV need to be screened for vasculopathies. Echocardiography and carotid artery Doppler are useful screening tools in patients presenting with stroke.\(^7\)

Previously the survival was less than a year but now stabilisation of intracranial aneurysms has been shown with HAART and surgery in selected cases.\(^7\) It still has to be determined whether early treatment with HAART will prevent the occurrence of HIV vasculopathy.

It is clear from this overview that more information is required on the association between HIV and vasculopathy in children. This is an uncommon presentation of HIV, it may be AIDS defining or it may present as an immune reconstitution syndrome. There are similarities to Takayasu’s arteritis (multiple aneurysms and TB diagnosis in some cases) which might be linked to the pathogenesis. Overall, most patients improve on HAART and surgical therapy may also be considered especially for extracranial sites. The role of steroids has not been well defined. Multicentred studies and further research with long term follow up is necessary for us to have a better understanding of the disease and to improve the lives of children infected with HIV.
REFERENCES


48. Horn C. Takayasu arteritis. [Internet article] 2010. URL:


APPENDIX A

ETHICS CLEARANCE

Ethics clearance was obtained from the Wits Human Research Ethics Committee (Medical).

The protocol number is M070341.