# Surgical Intervention for HIV Related Vascular Disease

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**Objectives.** To determine the outcome of surgical intervention in patients with HIV associated vascular disease.

**Design.** Prospective clinical survey.

**Materials and methods.** Routine voluntary testing for HIV/AIDS was performed in patients who presented to our unit with peripheral vascular disease. One hundred and nine patients (5.7%) were prospectively identified over a 5-year period (2001–2006).

**Results.** 24 patients presented with aneurysmal disease whilst occlusive disease was present in 66 patients. There was not much difference between patients with aneurysmal disease and patients with occlusive disease as to age, CD4 count and other risk factors for vascular disease. The peri-operative mortality for aneurysmal disease was 10.6% versus 3.6% for occlusive disease ($p = 0.264$). Long-term mortality was significantly worse ($p = 0.049$) for patients with aneurysmal disease. The results of revascularization in occlusive disease were poor with a limb salvage rate of 31.6%. There was no significant difference in CD4 T-cell counts between primary amputation and revascularization groups ($p = 0.058$).

**Conclusion.** Patients with aneurysmal disease have a high peri-operative and long-term mortality and it appears that surgical intervention should be reserved for life-threatening aneurysms only. Patients with occlusive disease have a better survival rate but limb salvage is poor. Primary amputation may be preferable to bypass surgery in patients with critical limb *ischaemia*.

## Introduction

South Africa has one of the most rapidly growing HIV epidemics in the world[1] and [2] with an estimated 5.4–5.6 million HIV-positive people (UNAIDS/WHO AIDS December 2006).

There is a well documented relationship between vascular disease and HIV infection.[3], [4] and [5] These patients may present with occlusive disease, aneurysms, spontaneous arterio-venous fistula or the complications of hypercoagulability. They may also, however, present with the normal spectrum of vascular disease such as atherosclerosis or trauma where HIV positivity is an incidental finding. The aim of our study is to describe our experience with vascular surgery in HIV related vascular disease.[6]

## Patients and Methods

In January 2002 we started with a programme of routine voluntary testing for HIV/AIDS. Informed consent was obtained in over 90% of all admissions. Comprehensive screening for risk factors for atherosclerosis was carried out.

One hundred and nine patients were prospectively identified over a 5-year period with follow-up data available for 82% of patients. Patients who presented with vascular emergencies were managed regardless of their HIV status because this information was not available at the time of presentation. As no specific guidelines were available at the time, we based our elective management on immune status, taking the CD4 T-lymphocyte count into consideration. When the CD4 T-cell count exceeded 500, patients were managed according to standard vascular protocols appropriate for sero-negative patients. If the CD4 T-cell count was between 200 and 500, a conservative alternative to surgery was applied where possible. If surgery was unavoidable, however, we opted for a less invasive procedure, e.g. extra-anatomic bypass procedures such as axillo-femoral or femoro-femoral bypasses were used rather than the more invasive aorta-bifemoral bypass. In patients with established AIDS (CD4 T-cell

count < 200), palliative treatment was administered unless critical limb ischaemia necessitated primary amputation or surgery meant saving a life. Standard surgical techniques were used and no patients received endovascular treatment. Highly active antiretroviral therapy (HAART) in state hospitals became available in 2003, but was very slow to reach effective numbers and none of our patients were on active treatment.

## Results

We tested for HIV in 1905 patients whom presented to our unit with vascular disease. 109 Patients tested HIV positive (5.7%). Patients that were HIV negative had a very similar pattern of vascular disease as the rest of the Western world. Patient demographics are summarised in Table 1.

Table 1. Patient demographics (*n* = 109)

| | | |
|---|---|---|
| Race | Black | 99 (90.8%) |
| | White | 4 (3.7%) |
| | Mixed | 4 (3.7%) |
| | Asian | 2 (1.8%) |
| | | |
| Gender | Male | 88 (80.7%) |
| | Female | 21 (19.3%) |
| | | |
| Age | Age (mean) | 40 years |

Aneurysmal disease was present in 22% (24 patients) and occlusive disease in 61% of our patients (66 patients). Trauma accounted for 16 patients and 3 had spontaneous AV-fistulae.

Aneurysms were often multiple and in unusual anatomical locations. Sixteen patients had multiple aneurysms (Fig. 1). A young 30-year-old black man presented with a total of 101 small saccular aneurysms spread throughout his vascular system. A 46-year-old black male presented with multiple aneurysms in both internal and external iliac arteries, the right superficial femoral artery (SFA) and fibular artery, and a massive aneurysm in the left SFA. A 35-year-old black woman presented with two saccular aneurysms of her superior mesenteric artery. A 45-year-old black male presented with eight aneurysms distributed in the distal aorta, iliac, posterior tibial, subclavian and carotid arteries. The femoral (Fig. 2) and carotid arteries (Fig. 3) were most commonly involved.

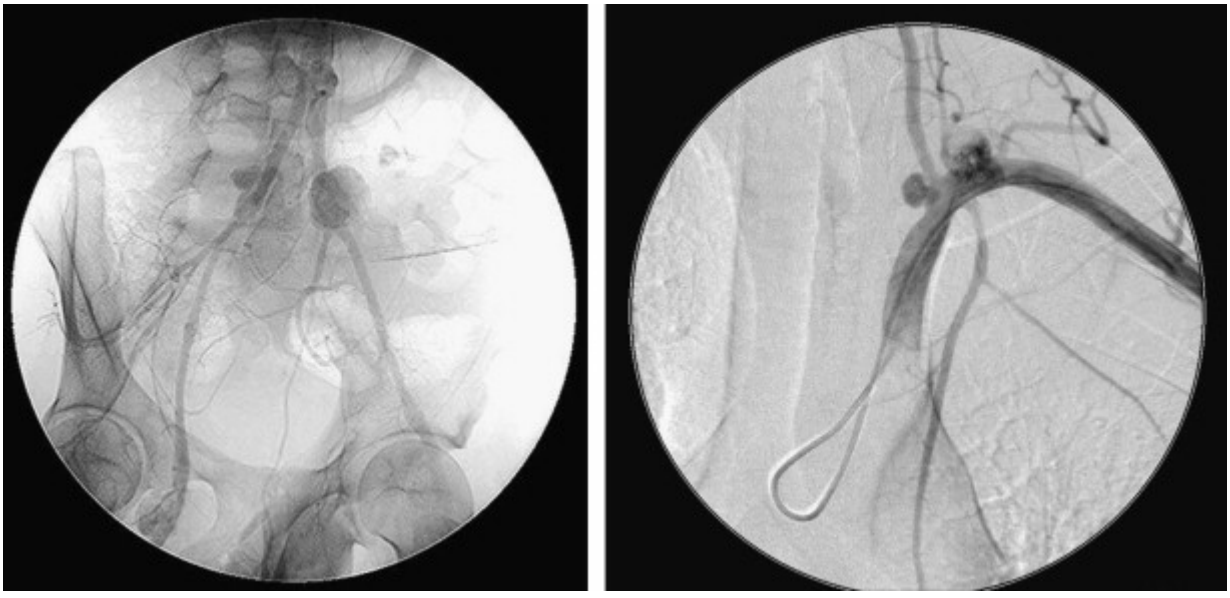

Fig. 1. 31-year old black patient with multiple saccular aneurysms.

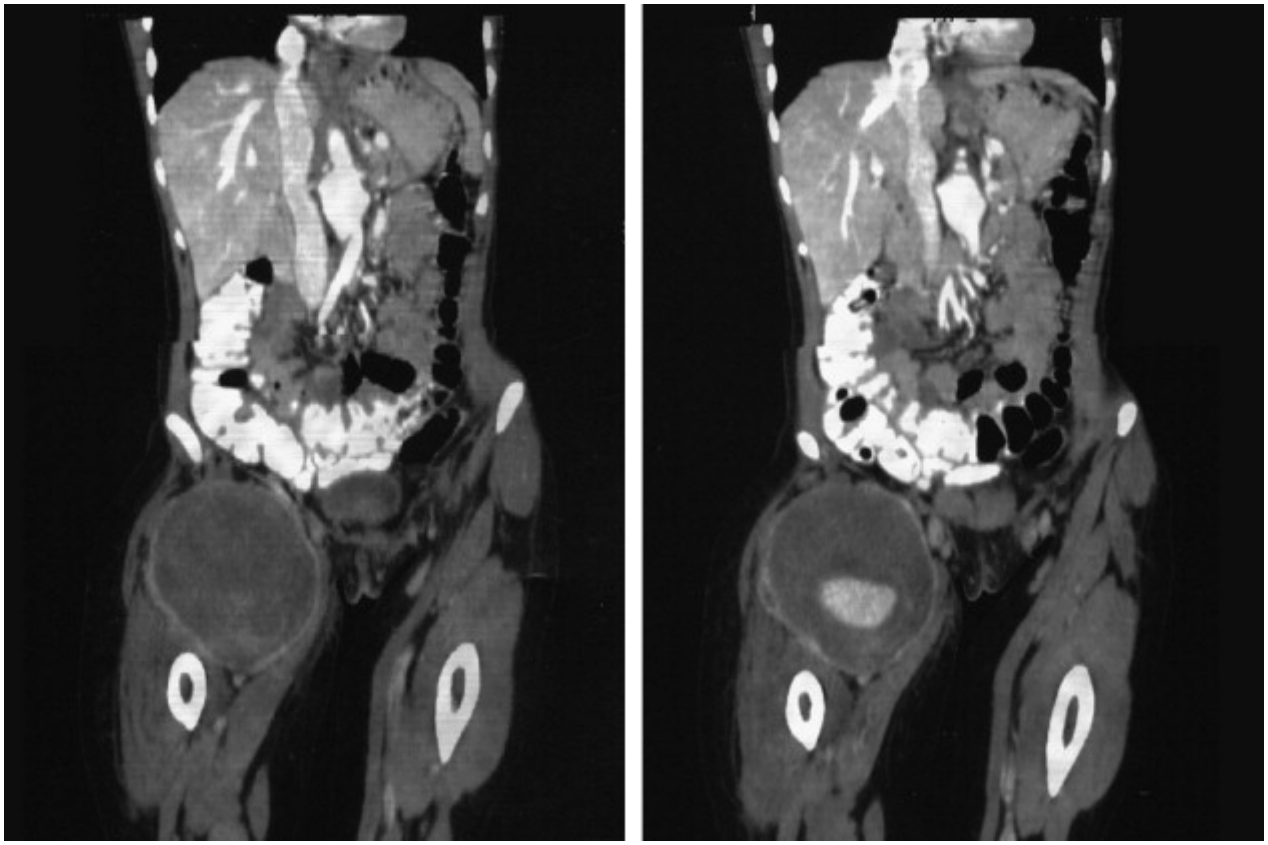

Fig. 2. 28-year old black female with femoral aneurysm.

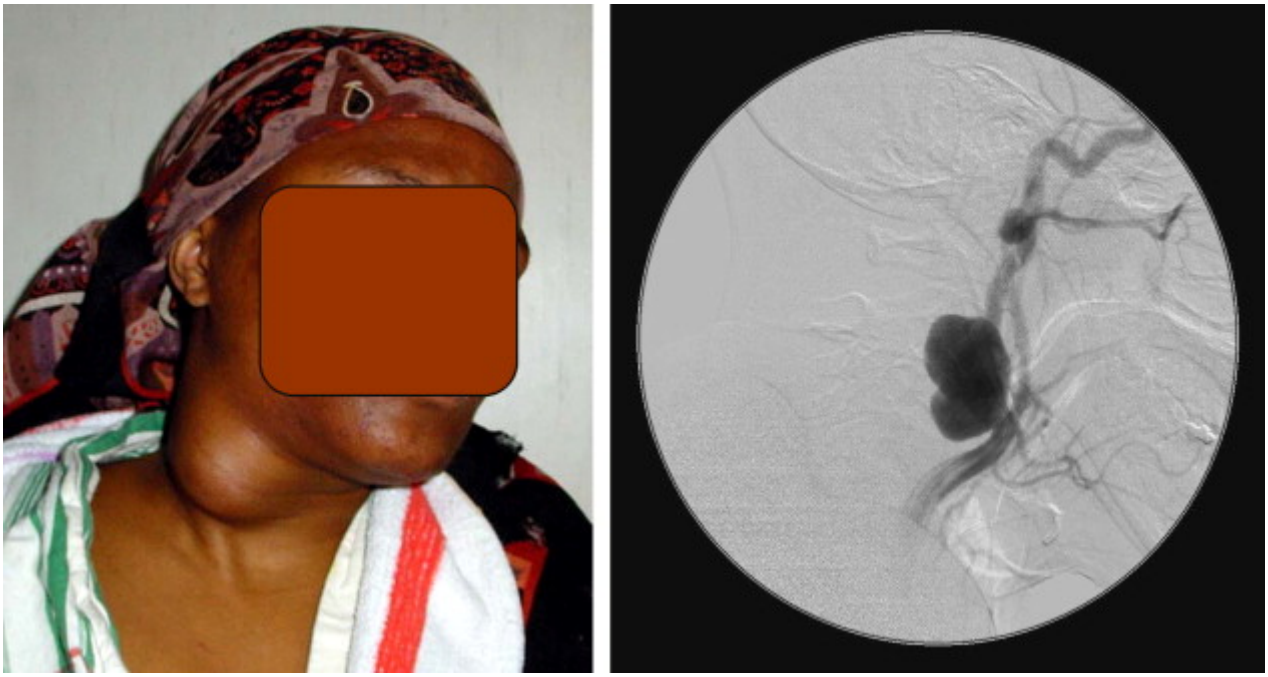

Fig. 3. 28-year old female with carotid aneurysm.

Occlusive disease was mostly diffuse with a fibro-obliterative appearance. There were long-segment occlusions with poor distal run-off which are generally not amenable to bypass surgery.

The treatment employed is summarised in Table 2.

Table 2. Treatment of 109 Patients

| | | |
|---|---|---|
| • Aneurysmal disease | | **24** |
| ○ Abdominal Aorta | | **3** |
| ■ Aorta-bifemoral graft | 1 | |
| ■ Aorta tube graft | 1 | |
| ■ Non-surgical management | 1 | |
| ○ Thoraco-abdominal | | **3** |
| ■ Non-surgical management | 3 | |
| ○ Femoral artery | | **9** |
| ■ SFA: Autologous vein interposition | 4 | |
| ■ SFA: Fem-pop → AKA | 1 | |
| ■ SFA: Repaired + Fem-fem | 1 | |
| ■ SFA + renal → Died before ø | 1 | |
| ■ SFA: Ligated | 1 | |
| ■ CFA: Prosthetic interposition | 1 | |
| ○ Popliteal artery | | **1** |
| ■ Bilateral autologous interposition | 1 | |
| ○ Superior mesenteric artery | | **1** |
| ○ Carotid artery | | **4** |
| ■ Ligated and excised | 2 | |
| ■ Repaired with prosthesis | 2 | |
| ○ Refused Rx (multiple locations) | | **3** |
| | | |
| • Occlusive disease | | **66** |
| ○ Aorta-bifemoral bypass | | **3** |
| ○ Femoro-femoral bypass | | **5** |
| ■ 2° Amputation < 6 months | 3 | |
| ○ Axillo-bifemoral bypass | | **5** |
| ■ Removed due to graft sepsis | 3 | |
| ○ Femoro-popliteal bypass | | **12** |
| ■ 2° Amputation < 6 months | 10 | |
| ○ Primary amputations | | **18** |
| ■ Above-knee (AKA) | 14 | |
| ■ Below-knee (BKA) | 2 | |
| ■ Hip disarticulation | 1 | |
| ■ Forearm | 1 | |
| ○ Thrombectomy with fasciotomy | | **9** |
| ■ Above-knee amputations | 6 | |
| ■ Lost to follow-up | 3 | |
| ○ Lumbar sympathectomy | | **4** |
| ■ Lost to follow-up | 3 | |
| ○ Non-surgical management | | **10** |
| | | |
| • Trauma | | **16** |
| • Spontaneous AV-fistula | | **3** |

There was a failure rate of >75% for bypass surgery, i.e. axillo-bifemoral, femoro-femoral and femoro-popliteal procedures. Patients who underwent thrombectomy also had disappointing outcomes. Primary amputations were done in 18 patients with a high percentage of local sepsis. They were treated on an outpatient basis and most healed within 3 months. Mean length of hospital stay in patients with primary amputation was shorter than in patients with failed bypass surgery and secondary amputation (7 vs. 21 days). Further analysis of patients with lower limb ischemia (aorta-iliac and femoro-popliteal distribution) is summarized in Table 3.

Table 3. Analysis of patients with lower limb ischemia

| | Aorta-iliac | Femoro-popliteal |
|---|---|---|
| (*n*) | 23 | 42 |
| Primary amputation | 6 (26%) | 12 (29%) |
| Surgical bypass procedure | 12 (52%) | 26 (62%) |
| Non-surgical (Cx) | 5 (22%) | 4 (9.5%) |
| Late amputation | 7 (41%) | 15 (50%) |
| Peri-operative mortality | 1 (5.5%) | 1 (2.6%) |
| Long-term mortality | 9 (50%) | 9 (26%) |
| Limb salvage | 5 (42%) | 7 (27%) |
| Lost to follow-up | 5 (22%) | 7 (17%) |

There was not much difference between aneurysmal and occlusive disease according to age: (mean 39.3 vs. 40.7 years); CD4 T-cell count: (mean 323.2 (79–916) vs. 300.2 (15–926)) and other risk factors for vascular disease. The peri-operative mortality was 10.6% for aneurysmal disease and 3.6% for occlusive disease. This did not reach statistical significance ($p = 0.264$; Fisher's exact test). Long-term mortality was significantly worse ($p = 0.049$; Log-rank test) for patients with aneurysmal disease (Fig. 4 and Table 4).

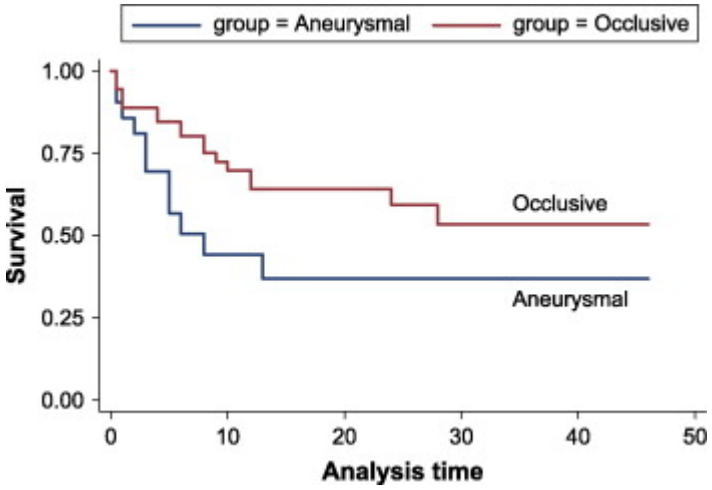


Fig. 4. Kaplan-Meier survival estimates, by group. Aneurysmal survival significantly worse than occlusive survival ($p = 0.049$; Log-rank test). Times are in months. Refer Table 4.

Table 4. Survival for aneurysmal disease is significantly worse than for occlusive disease ($p = 0.049$; Log-rank test). Times are in months

| Time | Total | Fail | Lost | Function | [95% Conf. int.] |
|---|---|---|---|---|---|
| Aneurysmal | | | | | |
| 0.5 | 21 | 2 | 0 | 0.9048 | 0.6700–0.9753 |
| 1 | 19 | 1 | 0 | 0.8571 | 0.6197–0.9516 |
| 2 | 18 | 1 | 3 | 0.8095 | 0.5689–0.9239 |
| 3 | 14 | 2 | 1 | 0.6939 | 0.4379–0.8507 |
| 5 | 11 | 2 | 0 | 0.5677 | 0.3123–0.7592 |
| 6 | 9 | 2 | 0 | 0.5046 | 0.2574–0.7085 |
| 12 | 7 | 0 | 1 | 0.4416 | 0.2067–0.6545 |
| 13 | 6 | 1 | 2 | 0.3680 | 0.1486–0.5920 |
| 37 | 3 | 0 | 2 | 0.3680 | 0.1486–0.5920 |
| 46 | 1 | 0 | 1 | 0.3680 | 0.1486–0.5920 |
| | | | | | |
| Occlusive | | | | | |
| 0.5 | 54 | 3 | 0 | 0.9444 | 0.8376–0.9817 |

| Time | Total | Fail | Lost | Function | [95% Conf. int.] |
|---|---|---|---|---|---|
| 1 | 51 | 5 | 7 | 0.8889 | 0.7693–0.9485 |
| 6 | 39 | 4 | 7 | 0.8022 | 0.6623–0.8888 |
| 9 | 28 | 2 | 1 | 0.7236 | 0.5681–0.8311 |
| 12 | 25 | 2 | 7 | 0.6411 | 0.4768–0.7657 |
| 18 | 16 | 0 | 3 | 0.6411 | 0.4768–0.7657 |
| 24 | 13 | 1 | 2 | 0.5918 | 0.4116–0.7334 |
| 28 | 10 | 1 | 3 | 0.5326 | 0.3366–0.6945 |
| 37 | 6 | 0 | 5 | 0.5326 | 0.3366–0.6945 |
| 46 | 1 | 0 | 1 | 0.5326 | 0.3366–0.6945 |

Refer Fig. 4.

Due to the skewness of CD4 T-cell count data, geometric means and 95% confidence intervals are reported as descriptive statistics. Comparisons were done using analysis of variance for ranks and neither primary amputation versus revascularization patients ($p = 0.058$), nor secondary amputation versus limb salvage from the revascularization group of patients ($p = 0.151$) differed significantly. The CD4 T-cell count also did not differ significantly between survivors and non-survivors ($p = 0.227$; Student's two-sample t-test). Twenty-eight patients had a CD4 count of <200. Ten of these were still alive at the time of writing with follow-up ranging from 12–48 months (a survival of up to 4 years without HAART), five were healthy at follow-up of less than a year, seven died within a year and six were lost to follow-up.

## Discussion

HIV-associated vascular disease is a specific disease entity which differs from atherosclerotic disease in various aspects.

HIV positive patients are younger with an average age of 40 years in comparison to 55–74[7] years in patients with atherosclerotic disease. There is also a lower incidence of the typical risk factors:

• Smoking: Although the incidence of cigarette smoking was the same as in the atherosclerotic population, fewer cigarettes were smoked per day: average of 5–10 cigarettes per day;

• Hypercholesterolaemia: 2% vs. 65%;[7]

• Diabetes mellitus: 2% vs. 18%;[8]

• Hypertension: 21% vs. 35–55%.[9]

HIV-related aneurysms have several histological features distinguishing them from degenerative and infective aneurysms. The principal feature is occlusion of the vasa vasorum by an inflammatory cell infiltrate, usually a leucocytoclastic vasculitis with proliferation of slit-like vascular channels within the adventitia. Weakening of the vessel wall due to the arteritic process usually results in the formation of saccular type aneurysms.[10] and [11]

Du Pont's first report on aneurysms associated with HIV was followed by many publications dealing with this issue.[5], [12], [13] and [14] HIV-associated aneurysms are typically multiple and often occur in atypical locations with a predilection for the carotid and superficial femoral arteries.[15] and [16] Defining the role played by HIV itself is complicated by the diverse opportunistic infections known to be associated with vasculitic syndromes such as Epstein Barr, hepatitis and cytomegalovirus. Some aneurysms are associated with an infective agent, but cultures from our patients were negative.

The results from our 5-year prospective study show an increase in young patients presenting with advanced limb ischemia (rest pain, ulceration or gangrene). Our patients mainly presented with multilevel occlusive disease. It is of a fibro-obliterative nature and is seldom amenable to bypass surgery due to inadequate run-off. Compared to patients with atherosclerotic disease, the results obtained in patients with HIV-associated occlusive disease were much worse.

These patients have characteristic angiogram findings of long-segment occlusions, pristine vessels proximally and poor or absent distal run-off. Chetty and Nair[10] proposed that occlusive disease occurs secondary to the same leucocytoclastic vasculitis of the vasa vasorum that causes large-vessel aneurysmal disease, i.e. bipolar clinical

expressions of the same pathological process. This is not dissimilar to other arteritic syndromes such as Takayasu's and Behcet's disease, where occlusive and aneurysmal forms of the disease occur with identical histopathological features. All these clinical presentations may be due to the direct and indirect effects on endothelial cells.

Although the precise pathogenesis of HIV-1 associated vascular disease is not clear, there have been advances in the understanding of the biochemistry and cell biology of these changes.[17] This is based on biological and molecular activation of **endothelial cells (EC)** in HIV-1 infection.

The direct effect on EC behaviour is selective impairment in storage and/or excretion of molecules such as endothelin-1 and Von Willebrand factor. The indirect effect on EC behaviour involves trans-acting transcription factor (Tat), a transcriptional activator of viral expression produced early after infection, which is essential for virus replication. During acute infection of T-cells by HIV, trans-acting transcription factor is released from the cells and activates a pro-inflammatory and angiogenic programme. Trans-acting transcription factor may compete with fibroblast growth factor (FGF) for binding to heparin sulphate proteoglycans of the cell surface and extracellular matrix and thereby activate EC (Tat angiogenic effect). Additionally trans-acting transcription factor binds to and activates the tyrosine kinase receptor encoded by vascular endothelial growth factor (VEGF) in EC and Kaposi's cells which induce vascular leakage and stimulate proliferation of EC.[17], [18] and [19]

Various factors influence the operative outcome of surgery in HIV-positive patients,[20] including immune status (CD4 T-cell count), opportunistic infections, WBC count, hematocrit, nutritional state (decreased albumin) and type of operation (emergency vs. elective; clean vs. contaminated).

The US government classifies AIDS using two criteria, namely the T-cell count and a history of AIDS-defining disease. Using the CD4 T-cell count as a parameter, patients are classified asymptomatic (≥500 cells/μL), Aids-related complex [ARC] (200–499 cells/μL) and AIDS (<200 cells/μL). Savoiz *et al.*,[21] and [22] Yii *et al.*,[23] and Consten *et al.*[24] showed that overall postoperative complications (mostly infection) with lower CD4 T-cell counts was as high as 39%. With CD4 T-cell counts above 500 the morbidity was 6%, which is comparable to that of HIV-negative patients.

To our surprise a significant number of our patients with a CD4 T-cell count of <200 survived longer than 1.3 years without HAART (average = 2 years), which is in contradiction with current literature.[25] Patients should therefore be individualised and not categorised according to the CD4 T-cell count as the only predictor.

The basic principles of vascular surgery also apply to HIV-positive patients. Autogenous vein is the preferred conduit, and if vein is not available, PTFE or polyester grafts are used. The commercially available silver-impregnated grafts are used if there is a high probability of sepsis. Savoiz[21] has shown that 35% of infective complications in HIV/AIDS patients are caused by opportunistic infections outside the range of normal vascular prophylaxis. These require therapeutic antibiotic and anti-fungal treatment according to microscopy, culture and sensitivity (MCS). In AIDS patients we recommend a broad spectrum antibiotic as prophylaxis and usually continue with co-trimoxazole for six weeks, unless MCS dictates differently. A single dose of fluconazole as prophylaxis against fungal infection is also routinely given to these patients.

We had no patients on highly active antiretroviral therapy (HAART), but in three patients, who received HAART for a period of 3 months in the private sector, the viral counts showed a marked reduction and there was a significant improvement in the CD4 T-cell counts. HAART has been shown in the literature to be effective in patients with advanced immune suppression.[26] Palella *et al.*[26] analyzed data on 1255 patients and showed a decline in mortality and morbidity attributable to the use of more intensive antiretroviral therapies. Multiple clinical trials have shown viral and immunologic efficacy of the newer HAART combinations by measuring the plasma load of HIV RNA and CD4 T-cell counts. There is, however, concern about patient compliance and the long-term adverse effects of the therapy. Currently accepted indications for HAART are summarized in Table 5.

Table 5. Indications for HAART therapy

| |
|---|
| • Symptomatic patients in clinical WHO stage 3 or 4 |
| • Asymptomatic patients with CD4 T-cell count <200 cells/μL |
| • CD4 T-cell count = 200–350 cells/μL (individualised, viral load > 100,000) |
| • Treatment should be deferred if CD4 t-cell count >350 cell/μL |

The most common side effects are haematological toxicity, hepatotoxicity, hyperlactataemia, hyperlipidemia, lipodystrophy and hypersensitivity. Peri-operative use of HAART at this stage, however, is limited to patients who require elective surgery that can be postponed for at least 3 months to reach the maximum benefit of increased CD4 T-cell count and decreased plasma viral load.

We are facing an increasing population with HIV and who may present with HIV associated vasculopathy. The dilemma that faces the vascular surgeon is when to intervene and what intervention is preferable. At the time when we started this study there were no clear guidelines. Although our patient numbers at present are still relatively small, we have learnt valuable lessons and think that we can make certain recommendations. The peri-operative morbidity and mortality of aneurysm repair is high with a poor long-term survival. Aneurysm repair should be reserved for life- and limb-threatening conditions. Limb salvage rate is poor in patients presenting with critical limb ischemia due to occlusive disease. The complication rate and length of stay was also more in patients who underwent secondary amputation after failed bypass surgery. We therefore think that primary amputation is an option to consider, especially in patients with additional aggravating factors.

CD4 T-cell count is not a good predictor of outcome and should not be used as the only criteria to determine management.

We have not employed endovascular techniques or used HAART during this study and the future use of these modalities may change the outcome. This is part of an ongoing study.

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