HIV DISEASE AND SURGERY

Human Immunodeficiency Virus disease and cardiac surgery – where are we?

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ABSTRACT

Uncertainties concerning the effects of cardiopulmonary bypass, outcome and possibility of operator injury slowed progress in cardiac surgery in the HIV-infected patient. Severely ill patients, some with AIDS and others probably with AIDS, formed the basis of early reports; it was shown they could be taken through surgery satisfactorily. Following the advent of antiretroviral monotherapy – zidovudine, an NRTI – in 1987, and dual therapy in the early 1990s with NRTIs, the addition of protease inhibitors (PI) in 1995, although a double-edged sword, led to triple therapy/ HAART, (2 NRTIs and a PI) and startling improvement in morbidity and mortality in markedly compromised HIV patients. Yet, it was only in 2003 when sizeable reports carrying ARV usage began to emerge. Intravenous drug addiction causing left-sided valvular heart disease was initially responsible for most cases, but there was now an increase in coronary artery disease (CAD) in young patients, blamed partly on lipid disturbances caused by PI. With an ARV roll-out in South Africa delayed to 2004, and PIs only used in second line therapy in State-administered treatment, the increase in coronary artery disease has not been noted. The need for surgery in pericardial disease is rare. Paediatric cardiac surgery has been rarely reported, but is locally carried out; a new approach to medical management of these children should lead to more frequent surgery. Heart transplantation lags far behind solid organ transplantation, but there are indications that it will be more readily accepted. Certain vascular pathologies appear to be peculiar to HIV, with the virus itself being able to enter vessel walls with evolution of vascular disease. PIs would appear to accelerate coronary artery disease, as seen in younger HIV patients, who develop abnormal lipid profiles. The approach to cardiac surgery in most cardiac teaching units is looked at. Many answers have been found, but new issues have also arisen, as in relation to ARV's and CAD. Most importantly, attitudes are changing: some would accept selected patients with AIDS not receiving ARVs. Very good results have followed surgery in patients who have suffered AIDS defining conditions but are stable on ARVs. SAHeart 2009; 6:210-221

Simple observation has made it clear that HIV is now a chronic disease. The massive impact of anti-retroviral therapy on life expectancy would imply that a recently diagnosed man of 25 years could expect to live a further 39 years.[1]

In this brief review the different aspects of cardiac surgery carried out, recognising that some units do vascular surgery as well, are discussed. Answers to some questions are clear; progress made, especially with the advent of the double-edged sword of anti-retroviral therapy, and changed attitudes, are considered.

VALVE SURGERY

The landmark paper by Frater and colleagues[2] in 1989 showed that human immuno-deficiency virus (HIV+) patients could be taken through surgery successfully. Striking features were: all but 1 of the 10 patients having 11 valve replacements, for infective endocarditis (IE) were intravenous drug addicts (IVDA), and, further, despite conventional medical therapy, 7 of these still had active infective endocarditis (AIE) at surgery (Table 1). In contrast, only 2 of 10 uninfected controls (HIV-) still had evidence of sepsis at surgery. One of the 7 with uncontrolled AIE died peri-operatively and 3 died of sepsis after completion of appropriate antibiotic therapy. Three with pre-operative control of AIE left

hospital clinically well, 1 dying of suspected but unproven AIDS at 41/2 months (Table 1). No prognostic markers were used; possibly some of these patients actually had AIDS, persistent sepsis perhaps being an indicator of immune deficiency. Frater et al.[3] suggested that surgery might not remove infection as it did in the HIV negative (HIV-). This paper raised more questions.

Yee (1991)[4] reported on 3 valve replacements and 3 coronary artery bypass grafts (CABG) in patients with AIDS, 3 being in extremis at time of emergency surgery. All survived surgery with a "benign" post-operative course. Three valve patients died with "fulminant AIDS" within 60 days. Yee questioned "the safety of cardiopulmonary bypass (CPB) in HIV-infected patients".

Cardiopulmonary bypass (CPB) was well known to cause a definite but transient depression of the immune system.[5,6] Frater's and Yee's papers did not answer the question whether the disease was worsened by cardiopulmonary bypass, but then theirs were of the sickest patients, and most compromised, one might take to surgery. Nevertheless, both thought life-saving surgery was warranted in these very ill patients. Concern about transmission of infection to team members was expressed.[2]

In 4 reports[7-9,11] of small numbers (Table 2), including patients with AIDS, according to CD4 counts and other markers, although progression to AIDS was seen, no-one was discouraged by their results: similar results as in HIV- could be expected,[11]

TABLE 1: Ten largest publications: Cardiovascular surgery in HIV+ patients using cardiopulmonary bypass (period from 1989 to 2008).

	Surgery With CPB	Markers	IVDA	Surgery	Indication Endocarditis	30 day Mortality	Complications	Late Mortality	Progression to AIDS	Survival
Frater 1989	10 patients 11 operations	---	9	V = 11	IE = 10 AIE = 7	V = 1	N/R	4 6-26 weeks	N/A	5 (12-30 months)
Aris 1993	39 patients 1 partial CPB	---	34	V = 38 CS = 1	IE = 33	V = 8 (20%)	N/R	8 (2 AIDS)	4 (9-60 months)	79% at 1 year* 48% at 5 years*
Everson Uip 1999	30 patients	---	N/R	V = 8 CS = 15 CHD = 5 Peric'l = 2	N/R	2 (6.6%)	"Same" as uninfected	6 (4 AIDS)	5 (1-74 months) (2 Peric'l)	19/25 alive 13-74 months
Mestres 2003	29 patients +2 off pump 35 operations	CD4 in 19 CD4 6-600 CD4 mean 289	24	V = 26 CS = 5	AIE = 21	V = 7 (23%) (5 AIE)	10	V = 9	3	65% at 1 year 42% at 3.4 years
Trachiotis 2003	34 patients +3 off pump	CD4 106-560 CD4 mean 360 VL higher in Vs	N/R	V = 10 CS =27	IE = 8 AIE = 6	V = 1 (2.7%)	22	0	0 Mean 2.4 years	100% Mean 2.4 years
Tec Chong 2003	22 patients	CD4 in 2 N/R	16	V = 22	IE = 20 AIE = 16	V = 1 (4.5%)	3 (only serious ones recorded)	10	0	40% at 5 years 20% at 8 years
Blyth 2006	49 patients 50 operations	CD4 in 42 CD4 37-1245 Average 685	0	V = 45 CS = 3 Other = 2	IE = 10 AIE = 6	V = 3 (6%) (1 AIDS)	16	8 (3 AIDS)	5	N/R
Filsoufi 2006	25 patients	CD4 in 25 CD4 51-1050 CD4 <500 in 17	17 Ao = 3	V = 15 CS = 7	IE = 14 AIE = 4	V = 1 (4%) (CD4 125)	9	3 (V = 1)	N/R	92% at 1 year* 86% at 3 years*
Castillo 2008	37 patients +2 off pump	CD4 in 39 CD4 mean 490 CD4 <500 in 22	24	V = 22 CS = 12 Ao = 5	IE = 16 AIE = 9	V = 2 (5%) (1 AIE)	12 0 in isolated CS	N/R	N/R	91% at 1 year 81% at 5 years (estimated)
Boccara 2008	27 patients	CD4 in 27 CD4 mean 502 VL <50 in 25	0	CS = 27		0	18	2	N/R	92% at 41 mo

*IE - infective endocarditis, mo - months, VL - viral load, AIE - active infective endocarditis, V - valves, IVDA - intravenous drug abuse, CHD - congenital heart disease, N/R - not recorded, Ao - aortic surgery, CPB - cardiopulmonary bypass, Peric'l - pericardial surgery, CS - coronary artery surgery, * - actuarial.*
Patient numbers for AIE, although noted separately, are included in the numbers given for IE.

CD4 counts of 300 cells/microL as entry to surgery were suggested.[8] Flum et al. (1997) for the first time reported on 2 cases – their 4 cases being coronary surgery cases - receiving antiretroviral therapy in the form of zidovudine, prior to cardiac surgery.[11]

Aris et al.,[10] in 1993, in the biggest series to date, of 40 patients (1 with partial CPB), set out specifically to determine if CPB has an accelerating effect on progression of HIV disease (Table 1), and found progression of disease was similar in an HIV group not having cardiac operations. CPB did not appear to hasten progression to AIDS. Similarly Everson Uip et al.[12] (Table 1), in the first paper from a developing country (1999), reporting on 30 patients, came to the same conclusion. They saw no increase in postoperative complications in HIV patients.

Mestres et al.,[13] in 2003, following an initial report (Miro et al.,[14]) reviewed long-term outcome in 31 HIV patients, 24 being IVDAs, in their detailed paper. Mortality related to AIE was 23.4% (Table 1). Impairment of immunity was not seen. Importantly, they would now accept all referrals for surgery, irrespective of staging, unless there was some medical or surgical contra-indication.

The retrospective report by Trachiotis et al.[15] [refer to CABG below] is different in that, 28 of the 37 patients were on Protease Inhibitors, pre- and post-operative CD4 cell counts were analysed and they looked specifically as to whether HIV patients were at greater risk due to immune depression, whether surgery increased progression to AIDS, whether the benefit of surgery was diminished by the disease, and whether the team was at real risk for acquiring infection (Table 1). Six of 10 valve patients, CD4 counts 106-480 cells/microL, were receiving Protease Inhibitors (PI). With 1 death and 7 complications, pre-and post-operative CD4 counts were not significantly different. Opportunistic infections (OI) did not occur during a mean follow up of 2.4 years. They found favourable answers to their questions. Benefit of surgery was clear. The significant increase seen in cholesterol levels after commencing PI, was a cause for concern.

Tec Chong et al.[16] (2003) in a 10 year retrospective series, with 16 of 22 patients undergoing valve replacements being IVDA, 16 with AIE, encountered 3 major complications and 1 death soon after discharge. Seven had died by 1.2 years. (All the IVDA were dead by 8 years) (Table 1). HIV patients with IE would have good early outcome; recurrence of IE related to continued IVDA (as in 5), rather than a compromised immune system. Progression of disease was not reported, and ART not used.

Blyth et al.[17] (2006) reviewed 49 patients undergoing mainly valve surgery between May 1995 and April 2003, in the first cardiac surgical paper from Africa (Table 1). These patients differed from those in other reports in that IVDA was not encountered, IE was uncommon and most patients were female. Early mortality was 6% for 50 procedures, with a complication rate of 34.7%. CD4 cell counts taken in 43 (range 37–1245 cells/microL) were not all available, as for emergencies, pre-operatively. Seemingly, active infective endocarditis in the markedly compromised, but small number (6) having emergency surgery, would lead to poor outcome: 4 of 6 emergencies for AIE, all 6 showing features of AIE at surgery, similar to Frater's experience, died. Three patients, all undergoing emergency valve surgery for AIE, had CD4 counts of < 250 cells/microL: 2 with counts of 37 and 204 died at 10 days and 3 months respectively, the latter with suspected endocarditis, whilst the third, with only one available count of 81 at 1 month died at 3 months, the cause not being determined. The overall outcome in this series (41 leaving hospital in NYHA Class 1) was similar to that in the uninfected. No patient received ARV therapy. Cardiopulmonary bypass could not be said to hasten progression of disease.

Filsoufi et al.[18] (2006) reported on 25 patients, 17 IVDA, and 13 receiving anti-retroviral/s (ARVs) (Table 1). Of 15 valve replacements, 1 (CD4 cell count 125 cells/microL, not on ARV's) died, with complications (9) occurring in 5 valve patients with pronounced risk factors. With 1 late valve death - a patient with AIDS on HAART – 3 year survival was >80% overall, "no significant differences" being found in comparing results in a similar uninfected cohort. Outcome of CABG was excellent. They concluded that surgery in patients with AIDS should be undertaken.

Castillo et al.[19] (2008), reviewed their experience with 39 patients (2 off-pump), 28 receiving HAART. CD4 cell counts were <500 cells/microL in 22 patients (Table 1). One early death (fulminant AIE) and 12 complications occurred, being limited to "high risk" groups (8 aortic and valve surgery patients). Plotted survival at 5 years was 81%. These very good results may be related to the use of ARV's/HAART and the fact that fewer patients are apparently presenting with AIE – a difficult entity in its own right.[13,19] They considered it practical to offer HIV+ as well as AIDS patients cardiac surgery with expectation of a good outcome, in view of the longer life expectancy related to ART usage.

CORONARY ARTERY SURGERY/CORONARY ARTERY BYPASS GRAFTING

By 2006, only Everson Uip et al.[12] and Trachiotis et al.[14] had reported sizeable numbers of isolated coronary bypass graft operations. Usually CABG, in small numbers, only formed a part of reports.

Yee[3] in 1991 had first reported on 3 CABG in "AIDS patients", 1 combined with an aortic valve replacement. All came through surgery well, but 2 developed OI, 1 dying. Two were well at 9 and 12 months. Flum et al's.[11] 4 patients, reported 1997, with CD4 counts >350 cells/microL , came through surgery well, but showed a reduction in CD4 cell counts, and progression of disease, 2 developing AIDS, during follow up of 7–49 months. (Table 2) Everson Uip[12] (1999) had excellent results: 10 of 12 CABG were asymptomatic at follow-ups extending from 16 to 74 months; 1 had AIDS at 24 months. Mestres et al.[13] in 2003 reported on 5 CABG, 4 with mean CD4 cell counts of 142 cells/microL (3 <200), all receiving ARVs, with excellent outcome but noting the abnormal lipid profiles, expected an increased surgical need for CABG due to ARV's.

Occasional case reports of CABG in patients with AIDS on and off-pump, on PI showed good results, but alluded to the expectation of increased premature coronary artery disease with increase in age and use of PI.[13, 20-23]

Trachiotis et al.[15] (2003) reported on 27 isolated CABGs, 3 off-pump; the largest detailed series which also included 10 valve procedures, 2 with CABG. Thirty–three percent of the CABG versus 40% of the valve patients had displayed AIDS-defining features, the latter having statistically higher mean viral loads (VL). Twenty-three CABG patients were on protease inhibitors (PI). Young males predominated. One valve surgery patient died peri-operatively. No late deaths occurred during a mean follow-up of 2,4 years and no patient progressed to AIDS. Complications were mainly infective; infective complications were thought to be more common than in the uninfected (HIV-). Noting the apparent PI related significant increase in cholesterol levels, they expect an increase in coronary artery disease (CAD) that will require surgery. This report clearly showed the excellent outcome that can be achieved in carefully chosen patients adherent to ARV's and stable. While noting that the questions posed were favourably answered, they stressed the need for managing the side effects of PI therapy on lipid profiles.

Totally endoscopic CABG on an HIV patient has been reported.[24]

In the first but small case-controlled study Jimenez-Exposito and others[25] (2006) compared 7 isolated HIV+ CABGs with 21

TABLE 2: Conclusions from 4 small series which included AIDS cases

Name	Date	Surgery	IVDA	AIE	Early Death	CPB worsens outcome?
Sousa Uva	1992[7]	10-9 V		3AIE, 3AIDS	1	No firm conclusions
Lemma	1992[8]	6 V	6	6 IE, 2AIE	1	No significant change in CD4
Brau	1992[9]	4V	4	2AIE, 1AIDS	0	No adverse effect on HIV
Flum	1997[11]	4CS	-	-	0	Significant CD4 count fall seen

IVDA - intravenous drug abuse, AIE - acute infective endocarditis, IE - infective endocarditis, V - Valve surgery, CS - Coronary artery surgery

TABLE 3: Case Control Studies in CABG

	HIV +* Control	PI	Mortality	Complications	Progr.	MACE	PCI
Jimenez-Exposito	7 vs 21	4 6 on ARV	0* 1 control	57% in both gps	0	N/R	0*
Boccara	27 vs 54	22 26 on ARV	0* 0	66%* 68%	0	41%* 18%	35%* 11%

** - HIV+, PI - Protease inhibitor, Progr - Progression to AIDS, MACE - Major Adverse Coronary Event, PCI - Percutaneous Coronary Intervention.*

matched HIV- controls retrospectively. Mean pre-operative CD4 count was 340 cells/microL. Four of the six patients receiving ARVs were also receiving protease inhibitors. Disease progression was not seen, no patient needing further CS at a mean 30,1 month follow up. Sample size of HIV-infected patients was small and of younger age (Table 3). End points were lacking.

Boccara and colleagues[26] (2008) in a well-balanced multi-centre case-controlled study (FRISCA-2) matched 27 HIV+ patients against 54 HIV- patients undergoing CABG in the setting of acute coronary syndrome (ACS) (Tables 1 and 3). They aimed at determining the eventual prognosis in these patients. Of the 26 (96%) of the HIV+ patients on ARVs, 22 were receiving PI. Numbers of grafts were similar. At a 41 month median follow-up both major adverse coronary events (MACE) and the need for revascularisation by percutaneous intervention (PCI) were increased in the HIV group. PCI was required only on native vessels. They concluded CABG to be safe and feasible. A small but significant fall in absolute CD4 cell counts was seen, but complications and OI were not seen. They concluded that atherosclerosis associated CAD was accelerated in these young HIV patients and advocated appropriate medication and aggressive lifestyle management. Lipodystrophy syndrome was present in 19. (Table3).

PERICARDIAL SURGERY

Pericarditis is well recognised to occur in HIV+ patients, and pericardial effusions in the pre-HAART era were frequently seen late in the disease.[27] Early in the HIV disease history, 1990, an increase in the incidence of pericardial effusions coincident with a rise in HIV was noted in Tanzania.[28] A review article[29] (2000) would say pericardial effusions could be "a marker for end stage disease" as CD4 counts tend to be low, OI and malignancy (e.g. lymphoma) being more frequently responsible for effusions, which themselves rarely cause death. These patients in recent experience seldom present to surgeons, unless there is a concomitant bacterial infection, causing a septic pericarditis needing formal drainage. Constrictive pericarditis so commonly caused by tuberculosis in South Africa and despite the close association between tuberculosis and HIV, was not referred for surgery in the HIV+ patient (personal experience). Possibly these patients die before manifestation of constriction. Mayosi et al.[30] recently found in a multicentre study from Africa, and this lacked concrete diagnostic evidence, that "clinically evident HIV infection had a major impact on the death rate in patients" presumed to have tuberculous pericarditis (in line with the author's suspicion). However, pericardiotomy for recurrent effusion, some with AFB positive fluid cultures, and pericardiectomy for constriction (one calcified) have been reported, but in small numbers.[28,31] Flum et al. (1995, 1997) considered surgical biopsy and drainage of the pericardium in patients with AIDS to have "minimal therapeutic effect" and were of little diagnostic benefit.[11,32] Pericarditis has been less frequently seen with usage of HAART.[33]

PAEDIATRIC CARDIAC SURGERY AND HIV

Mother to child transmission of HIV infection appears to have a trimodal expression, 15% having a rapidly progressive disease.[34] Estimates from a pooled study from Africa suggested 35% of infected infants might not survive 1 year.[35] The virus itself does not appear to be teratogenic.

"Literature regarding cardiac surgery in pediatric patients is non-existent".[36] Everson Uip's series[12] listed 5 congenital heart

operations, but no details, other than 1 death at 4 months, the others being "asymptomatic" from 32 - 57 months. Theodore and colleagues[36] reported on total correction of Fallot's Tetralogy in a 4 year old who post surgery sustained an extradural haematoma with neurological features but recovered fully. CD4 cell counts and CD4/CD8 ratios at 3 months mirrored pre-operative counts. This surgery is performed in South Africa, but has not been reported.

The WHO in November 2008 advised that all infants (children <12 months) suspected of or exposed to HIV should be tested at 4-6 weeks and, if positive, be treated with ARV for the rest of their lives.[37] This should bring cases to the surgeon's door!

TRANSPLANTATION

The main concerns about heart transplantation in infected recipients have been (1) HIV infection is a chronic, progressive systemic disease, (2) that major drug interreactions between ARVs and immunosuppressants would occur and (3) that further depression by immune suppressants would result.[38] Stock and Roland[39] regarded the last concern as "a final major barrier to transplantation". Interestingly, some immune suppressants such as cyclosporine, also suppress the virus.
Discussion and reports have hinged mainly around kidney and liver transplantation, with only a few reports on heart transplantation; a computer search has yielded little information.

Tzakis et al.[40] in 1990 reported on 25 transplants that included liver, kidney and 5 heart transplants. HIV infection was either present or incurred at surgery (blood transfusion). Four of the 5 heart transplants were alive at mean follow up of 2,75 years. Paediatric patients had a better outcome with 1 of 10 dying of AIDS as opposed to 5 of 15 adults in that series. In 1990 the death, from AIDS, was reported of the first heart transplant in Italy, 6 years after transplantation, infection being established at surgery.[41] Calabrese et al.[42] in 2003 carried out heart transplantation in a man, diagnosed 4 years previously with AIDS (CD4 cell count = 20 cells/microL). He had received treatment for metastatic Kaposi's sarcoma, but infection was stable on ART with added PI, with a CD4 count of 250 cells/microL and undetectable VL, but he had developed a cardiomyopathy. Two years after transplantation clinical and cardiac status were good, but he had experienced 6 episodes of rejection. He was in fact, one of the authors of the paper!

Halpern et al.[43] as far back as 2002, in considering ethical arguments, HIV transmission and "burden of proof", felt it time to "remove barriers to transplantation" and not wait for "evidence of efficacy to emerge". Bisleri and colleagues[44] (2003), reporting on a selected patient with good outcome at 2 years, proposed that heart transplantation should be reserved for those with CD4 counts in normal range, an undetectable VL and absence of past OIs.

In 2004 Pelletier and colleagues,[45] in reviewing transplantation in the HAART era and noting the reluctance to include HIV+ recipients, pointed out that many patients were accepted, particularly for liver transplantation, from groups known to have poor prognosis. From the (American) Scientific Registry for Transplant Recipients* they found only 20 patients undergoing heart transplantation between January 1999 and July 2004 (Table 4*).

Uriel et al.[46] discussed 7 patients, 5 HIV+ prior to heart transplantation, and 2 found to be HIV+ 1 and 7 years after transplantation. CD4 counts were all above 300 cells/microL. No complications and no OIs occurred during intermediate follow up. HAART was administered to 6 of these patients. (2009)

Of note is that last year, in South Africa, 2 kidneys from an HIV+ donor were transplanted into 2 HIV+ recipients with good immediate outcome. The American state of Illinois, the first state

TABLE 4: Heart transplantation in HIV- versus HIV+ Cases 1994 – 2004 : SRTR Database; Pelletier et al.

	Graft Survival		Recipient Survival	
	1 year	3 year	1 year	3 year
HIV - Cases 9154	85.2%	78.4%	85.6%	79%
HIV + Cases 20	90%	60%	90%	90%

Survival at 4 years in HIV+ recipients fell to 40%, but numbers were small.

to do so, has legalised organ donation/receipt between HIV+ persons. In an information document, a large American medical aid equivalent, Blue Cross and Blue Shield of Massachusetts, Inc,[47] in a 2007-2008 update would extrapolate guidelines for kidney transplantation to any other organ, as set out by the British HIV Association and the British Transplantation Society Standards Committee. Patients with life expectancy of at least 5 years, with CD4 counts >200 cells/microL, undetectable VL, adherence to HAART, all for at least 6 months, as well no AIDS-definining illness after "successful immune reconstitution after HAART", would be suitable recipients.[46]

Guidelines set out by the Netherlands Society of Cardiology and Netherlands Assciation for Cardiothoracic Surgery consider HIV to be an active systemic infection, which would be a definite contraindication. Recognising availability of more information, but no long term follow up, they are doubtful about suitability in view of increasing donor shortages.[38]

Stock and Roland,[48] noting more frequent rejection episodes and the prolonged depression of CD4 cell counts after treatment for these, refer to improved and comparable results in solid organ transplantation in selected patients since initiation of HAART; rejection episodes are probably due to a dysregulated immune system.

Numerous issues, not the least being availability of organs and the unsatisfactory outcome prior to HAART, have delayed general acceptance of the HIV+ patient for transplantation. With the advances in ARV's, the expertise available in immunology and ARV and HIV management, it is likely that heart transplantation in HIV patients is not far from acceptance.

Cardiac transplantation in the HIV situation is under discussion in South Africa[49] where again, the advent of ARV/HAART was markedly delayed, and the Public Health System has failed.

SOME ASPECTS OF VASCULAR DISEASE AND ARV/HAART

Vascular

Joshi et al.[50] described a particular histological arteriopathy in blood vessels of children with HIV, one having aneurysms of the right coronary artery with myocardial infarction. Bayley[51] in 1990 reported peripheral gangrene, implying proximal arterial occlusion, requiring high amputation, in young HIV+ patients, in Zambia, while unusual multiple aneurysms of the aortic arch, brachiocephalic and subclavian arteries were encountered in Zimbabwe.[52] Nair et al.[53,54] (1997, 2000) encountered these entities locally: they felt that the histological similarities in the 2 conditions would have "a common pathogenetic event". In the absence of micro-organisms and atherosclerosis, it was suggested that the virus might directly involve the vessel.[54] Premature coronary artery disease has been noted in young HIV patients.[55,56] Tabib et al.[57] found distinctive histological features which they regarded as indicative of an accelerated process of coronary artery atherosclerosis in young HIV+ patients.

Endothelial dysfunction has been noted in HIV disease, as has hypertriglyceridaemia, hypercoagulability and coronary artery disease, even before the use of protease inhibitors.[58] Kamin and Grinspoon[59] in an editorial review in 2005 concluded that molecular and clinical studies would support the occurrence of vascular disease and endothelial dysfunction in HIV + individuals. In a study on porcine coronary arteries,[55] Tat protein which is an HIV regulatory protein was shown to interfere with endothelial relaxation in porcine arteries. This endothelial dysfunction may well relate to vascular disease.

The virus itself can enter the vessel wall and perhaps directly cause specific disease of the vessel wall: Scholtz[60] refers to a presentation in which Tudhope reported a high viral load in the arterial wall of an HIV+ patient whilst Barbaro et al.[61] found evidence of the virus in the coronary artery wall in a fatal case of myocardial infarction in a patient with HIV-associated coronary arteritis. Johnson et al.[62] from a literature review in 2003 concluded these patients may be predisposed to develop vasculitic

syndromes. Recently in a complex study in coronary artery tissue, Eugenin et al.[63] showed that the virus could enter smooth muscle cells (SMC), both in vitro and in vivo. Further in vitro work showed infected SMC would release a chemokine known to be a "critical mediator of atherosclerosis" - so the virus may possibly be involved in a tortuous pathway which would "explain the atherosclerosis and vasculopathy" seen in HIV disease. Interestingly, by looking at soluble endothelial and platelet activation markers in 3 matched HIV+ cohorts, (1) on protease inhibitors (PI), (2) on NNRTI (3) and treatment naïve patients, Francisci et al.[64] concluded that, in the short term at least, chronic HIV disease was responsible for changes in these markers of endothelial function, rather than ARV therapy. In contrast, Stein et al.,[65] by measuring flow mediated vasodilation in brachial arteries and measuring lipoproteins in PI treated versus treatment naïve patients, concluded that the "atherogenic lipoprotein changes" noted and endothelial dysfunction were attributable to protease inhibitors.

ARV AND HAART

In 1998, Palella and colleagues[66] reported on the dramatic fall in mortality and morbidity documented in the markedly compromised HIV+ patients as intensity of combination therapy, especially with the addition of protease inhibitors (PI), was increased. The Cascade collaboration[67] study supported these findings when comparing treatment before and after the introduction of HAART.

Also in 1998, Henry et al.[68] published a research letter, based on findings in 2 young men which led to a review of patients receiving PI, illustrating "premature coronary artery disease (CAD) with protease inhibitors". Carr et al.[69] described the syndrome of lipodystrophy, hyperlipidaemia and insulin resistance as seen in patients receiving PI therapy, whilst Periard and colleagues[70] demonstrated increased total cholesterol and triglyceride levels – "atherogenic dyslipidaemia" - in PI recipients. There appeared to be a distinct and disturbing dark side to protease inhibitors.

Duration of treatment was seen to have a direct bearing on the incidence of myocardial infarction, especially in men on PI for longer than 18 months.[71] The DAD study (2003)[72] showed a duration- related, relative rate increase in myocardial infarction; the absolute risk was low. Currier and colleagues[56] in a very large study determined the significantly increased risk in the young age group 18 to 33 years on ARV for developing coronary artery disease. In a follow on from their earlier observation, the DAD study group[72] confirmed that duration of PI usage related to myocardial infarction. In a smaller group on NNRTI this was not evident.

Triant et al.[74] in a study involving 3851 HIV patients and more than 1 million HIV-uninfected, found, in brief, a significant increase in acute myocardial infarction rates in the HIV patients on ARV.

Acute type B lactic acidosis, a well-recognised complication of NRTIs, has been reported after aortic root replacement in a patient on HAART.[75]

CARDIAC SURGERY IN SOME TRAINING UNITS IN SOUTH AFRICA

In answer to a simple questionnaire given to 4 units, information from a website and personal discussion, it is apparent that 5 units are operating on HIV+ patients, and with the exception of 1 unit , all cardiac surgeons were operating on these patients. Entry criteria were used by all, but differed; they were not always exactly defined, but all were based on CD4+ cell counts, general status and well-being of the patient, with use of ARVs playing a role. Two units did not routinely test all patients for HIV disease.

Thus, broadly:

CD4 cell counts, Clinical status and Elective Surgery (4units)

Unit 1: Patients with CD4 cell counts > 400 cells/microL were accepted, those with counts 200 – 400 were individualised with regard to absence of AIDS defining conditions and nature of surgery. Usually would refer those with CD4 cell counts < 200 cells/microL for ART. Would prefer all patients to be on ARV's.

Unit 2: Those with low CD4 counts (< 200 cells/microL) accepted but to be on ARVs.*

Unit 3: Patients with CD4 counts >200 cells/microL accepted for elective surgery* Those with counts <200 cells/microL, but otherwise well, referred for ARVs with aim to get CD4 count >200 cells/microL.

Unit 4: In view of a large past experience and review, patients with CD4 counts >200 cells/microL (previously >400) and without any stigmata of AIDS, are accepted. Patients on ARVs for more than 3 months, irrespective of CD4 count, otherwise well (no OI), accepted. Viral load (VL) would be considered.

Emergency surgery (5 units)

Emergency referrals for surgery would be accepted without CD4 estimation, or even HIV testing (by some), but would need to be free of AIDS-defining conditions and would need to fulfil general criteria for emergency surgery, as in uninfected patients.

Children (1 unit – all units not questioned)

Children younger than 18 months with CD4 to total lymphocyte (CD4/TLC) percentage >20%, or receiving ARVs for longer than 3 months and children older than 18 months with a CD4/TLC percentage >15%, or on ARV's for longer than 3 months would have surgery.

*Advanced AIDS would exclude patients

SOME ANSWERS

From this brief review of cardiac surgery (and vascular surgery) in HIV+ patients many answers are apparent. The initial one concerning further depression of the immune system by cardiac surgery and CPB was clear some years ago: depression caused is transient[5,6] and even those patients with advanced disease tolerate surgery well.[2,4,7-9,13,17,20,23]

HIV disease is recognised as a chronic disease and even without ARV therapy, life expectancy from time of seroconversion is at least 10 years. Acceleration of disease progression in relation to cardiac surgery has not been shown. With advances in ARV therapy and expert care, and those are certainly available in South Africa, good life expectancy can be further extended.[1] The expected high peri-operative mortality and morbidity rates have not consistently occurred, and results are very similar to those in the uninfected.[12,17] Even Frater's initial early experiences in sick IVDA with AIE (some possibly with AIDS) not responding to appropriate antibiotic therapy, and especially Yee operating on what he called "AIDS patients", showed these patients could get through surgery.[2,4] OI in Yee's patients could not be blamed on surgery or CPB. Certainly the type of patient and the nature, stage and severity of the illness, as in all surgery, would have bearing on outcome. More recent experience with AIE in IVDA does not reflect results of the first reports.[16] AIE is more likely in IVDA than other HIV patients, with left sided valves most commonly requiring surgery.[2,16,19] Our experience was, in the absence of IVDA, that IE and AIE were not common, and when seen occurred more commonly in patients with low CD4 counts, left-sided valves being affected; these patients did not fare well.[17] Reportedly, IE in IVDA more commonly affects the tricuspid valve, and generally has a good outcome, while left-sided IE runs a worse course and mortalities of 5-15% could follow surgery. HIV+ IVDAs with CD4 cell counts <200 cells/microL, suffered significantly increased mortality.[14] This perhaps explains Frater's early experience.[2] IE in IVDA is now less frequently seen.[13,18] Recurrent IE in IVDA relates to a return to drugs rather than immune compromise.[2,13,16]

Based on limited available reports, CABG has better results than valve surgery[18,19] and can be done less invasively. More cases are being referred, possibly due to PI usage and disturbed lipid profiles.[13]

Concern about surgical injury to the surgeon is real, but no record of a member of a surgical team having become infected after injury has been found. Techniques to avoid injury are well described; post exposure prophylaxis (PEP) must be available (although not pleasant!). Personal observation would indicate that there is still reluctance in some to operate on these patients.

Acceptance for surgery has changed, so that some will now accept all patients, provided they do not have some other

medical or surgical contra-indication to surgery; this will include patients not on ARV's.[13] Some would want ARV usage to reduce VL, patients to be in a stable state and would seemingly accept patients with AIDS.[15,18,19] The very good results emerging in the immediate and medium term in the HAART era (post-1996) would support this. Surgery in the carefully assessed patient with AIDS, not on treatment, in the absence of OI and standard contra-indications for surgery would now seem practical, immune reconstitution and initiation of ARV therapy being born in mind.

Reports on cardiac surgery in patients receiving ARV/HAART are few. The use of ARV's and especially HAART has altered this disease remarkably: not only has expected lifespan of the infected been improved but once immune reconstitution has taken place, OI are, at least, reduced and quality of life improved.[65,66] This has an impact on surgery.[15,19]

Drug side effects and effects of the disease itself, as discussed, on available evidence, do alter the lipid profile and lead to vascular and particularly coronary artery disease. This would require monitoring of lipids and careful use of cholesterol lowering medication as well as indicators of inflammation – an aspect beyond this paper.

There has been little discussion about type of valve to be used. Some have used from homografts to mechanical valves,[10,13] others favoured mechanical valves.[16,17] It seems reasonable to follow the protocol used in the uninfected of bioprosthetic valves in the older population (>65 years), and mechanical valves in those younger, knowing the early deterioration of bioprosthetic valves in young patients.[17] Homografts would have a role to play in IE involving the aortic root.

The use of prognosticators such as CD4 cell counts and VL are essential in HIV disease management: CD4 cell counts contribute to staging of disease, whilst VL in those on ARVs reflects success of viral suppression. This author strongly advises informed HIV testing for all potential cardiac/vascular surgery patients, especially where the result will influence management and subsequent outcome.

The earlier use of ARVs, where waiting lists are the order of the day, has been suggested[17] to allow for stability and improvement in cases with low CD4 cell counts. In South Africa, according to current national guidelines (under revision) ARV's are only advised once CD4 count is <200 cells/microL, or in case of an AIDS-defining illness. Most infectious diseases specialists in South Africa would start potential elective cardiac/vascular surgery patients on ARV's with CD4 counts <350 cells/microL. Mortality is nevertheless greater in these patients than in the uninfected.[1]

Tragically, most of the South African HIV community was denied anti-retroviral treatment for many years…

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