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CLINICAL RESEARCH

Contribution of the human immunodeficiency virus/acquired immunodeficiency syndrome epidemic to *de novo* presentations of heart disease in the Heart of Soweto Study cohort

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Aims The contemporary impact of the human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) epidemic on heart disease in South Africa (>5 million people affected) is unknown. The Heart of Soweto Study provides a unique opportunity to identify the contribution of cardiac manifestations of this epidemic to *de novo* presentations of heart disease in an urban African community in epidemiological transition.

Methods and results Chris Hani Baragwanath Hospital services the >1 million people living in Soweto, South Africa. A prospective, clinical registry captured data from all *de novo* cases of heart disease presenting to the Cardiology Unit during 2006–08. We describe all cases where HIV/AIDS was concurrently diagnosed. Overall, 518 of 5328 *de novo* cases of heart disease were identified as HIV-positive (9.7%) with 54% of these prescribed highly active anti-retroviral therapies on presentation. Women (62%) and Africans (97%) predominated with women being significantly younger than men 38 ± 13 vs. 42 ± 13 years ($P = 0.002$). The most common primary diagnosis attributable to HIV/AIDS was HIV-related cardiomyopathy (196 cases, 38%); being prescribed more anti-retroviral therapy (127/196 vs. 147/322; odds ratio 2.85, 95% confidence interval 1.81–3.88) with higher viral loads [median 110 000 (inter-quartile range 26 000–510 000) vs. 19 000 (3200–87 000); $P = 0.018$] and a lower CD4 count [median 180 (71–315) vs. 211 (96–391); $P = 0.019$] than the rest. An additional 128 cases (25%) were diagnosed with pericarditis/pericardial effusion with a range of other concurrent diagnoses evident, including 42 cases (8.1%) of HIV-related pulmonary arterial hypertension. Only 14 of all 581 cases of coronary artery disease (CAD) (2.4%, mean age 41 ± 13 years) were confirmed HIV-positive.

Conclusion Cardiac manifestations of HIV/AIDS identified within this cohort were relatively infrequent. While HIV-related cardiomyopathy and pericardial disease remain important targets for early detection and treatment in this setting, HIV-related cases of CAD remain at historically low levels.

Keywords HIV • AIDS • Cardiovascular disease in Africa • Cardiomyopathy • Pericardial effusion

Introduction

Human immunodeficiency virus (HIV) infection is a pandemic affecting over 30 million individuals worldwide and accounting for more than 2 million deaths annually. Significantly, more than two-thirds (22 million) of HIV-infected people live in Sub-Saharan Africa. Per capita, South Africa is one of the worst affected countries with >5 million people being infected with HIV.[1] Human

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immunodeficiency virus/acquired immunodeficiency syndrome (AIDS) presents one of the foremost challenges in medicine as HIV directly affects the entire immune system and multiple organs with neurological, renal, pulmonary, and cardiac manifestations. It also indirectly affects multiple systems through opportunistic infections and/or neoplasm in addition to complications arising from its treatment. Although premature coronary artery disease (CAD) in patients with HV/AIDS has evoked concern in high-income countries in the post-antiretroviral therapy era,[2–4] the most commonly reported cardiac manifestations of HIV/AIDS in Sub-Saharan Africa are cardiomyopathy, pericardial disease (often related to tuberculosis), and pulmonary hypertension.[5] In the region, <20% of those who need highly active anti-retroviral therapy (HAART) receive it,[1] but this proportion will undoubtedly change and it is possible that cardiac manifestations of HIV/AIDS will alter accordingly. However, in this rapidly changing environment, our reliance on historical reports that focus only on specific cardiac manifestations and/or HIV-positive cases provides limited insight into the relative contribution (and subsequent challenges) of HIV/AIDS to a parallel and evolving epidemic of non-communicable and communicable forms of heart disease in the region.[6]

As the largest and most comprehensive study of *de novo* cases of heart disease in Sub-Saharan Africa to date, the *Heart of Soweto Study*[7,8] represents a unique opportunity to (i) confirm previous observations on the pattern of HIV/AIDS-related heart disease and (ii) provide additional insights into the nature and acuity of related case presentations; particularly within a background of epidemiological transition towards the types of heart disease (e.g. hypertensive heart disease,[9] a broad range of heart failures,[10] and atrial fibrillation)[11] typically seen in more affluent countries. We therefore examined the *Heart of Soweto* clinical registry to examine the relative contribution and impact of the HIV/AIDS epidemic on *de novo* manifestations of heart disease. We also sought to determine the potential impact of concurrently prescribed HAART.

Methods

Ethics statement

Ethical approval for the study was given by the University of the Witwatersrand Ethics Committee. The study conformed to the principles outlined in the Declaration of Helsinki. Due to the nature of the setting (an extremely busy hospital clinic and low levels of English literacy), each patient verbally agreed to participate at the time of data collection and was assigned a unique identifying code (nine digits) to maintain their anonymity. Information on HIV status was collected according to general South African recommendations and practice.

Study setting

The *Heart of Soweto* Study is investigating emergent heart disease and its antecedents due to epidemiological transition in the geographically compact townships that comprise Soweto (estimated population of 1.1 million people of mainly African descent) and surrounding communities in South Africa.[12] The purpose and methods of this study, including a detailed clinical registry of nearly all newly diagnosed cardiological cases presenting to the 3500 bed Chris Hani Baragwanath Hospital, have been described in detail previously.[7,8] The hospital admits more than 125 000 patients per annum and is a key barometer of the overall health of its surrounding community. The specialist Cardiology Unit manages around 21 000 cases per annum and applies gold standard cardiological expertise and advanced investigations to provide definitive diagnostic and treatment services. The underlying strengths of what is still sub-Saharan Africa's largest and most comprehensive study of heart disease to date are as follows: (i) systematic clinical profiling with all patients presenting to the Cardiology Unit subject to echocardiography and cardiologist review and further investigations (e.g. coronary angiography) according to clinical profile and (ii) all cases were independently reviewed and classified according to prospectively applied criteria.

Study cohort

We describe identified cases of HIV/AIDS among all 5328 *de novo* presentations of heart disease and other cardiovascular disease (CVD) presenting to the Cardiology Unit during 2006–08 (overall, there were 6006 case presentations with 678 cleared of any form of CVD).[8] The cohort includes those referred for a cardiac assessment from the 12 local Soweto primary care clinics, in addition to those referred from the general medical outpatient facilities, the specialist medical registrar clinic, and diabetic clinic within the hospital. It also comprises patients initially admitted to the general medical, or any other ward at the hospital, referred for a cardiological consultation. All patients over 14 years of age are considered 'adult'. Where possible, we adhered to STROBE guidelines for studies of this type.[13]

Study data

Comprehensive demographic and clinical data were collected, as described previously.[7,9] This included New York Heart Association (NYHA) functional class and estimated glomerular filtration rate (eGFR), calculated using the modification of diet in renal disease-abbreviated formula: eGFR mL/min/1.73 m^2 = 186.3 × (serum creatinine mg/dL)$^{1.154}$ × (age)$^{-1.154}$ × (0.742 female sex) × (1.21 if black African) using serum creatinine concentrations (μmol/L) converted to mg/dL. A 12-lead ECG was performed and subject to blinded assessment using Minnesota coding.[14] Detailed echocardiographic assessment of ventricular function, valve integrity, and function and regional wall abnormalities were available in all but 731 cases. Specifically, two-dimensional targeted M-mode echocardiography with Doppler colour flow mapping was performed, using a Hewlett Packard Sonos 5500 echocardiograph, attached to a 2.5 or 3.5 MHz transducer and measured to the American Society of Echocardiography guidelines.[15] These were used to derive left ventricular ejection fraction (LVEF), left ventricular end-diameter at diastole (LVEDD), left ventricular end-diameter at systole (LVESD), and right ventricular systolic pressure (RVSP). Every patient (regardless of age) with clinical suspicion of CAD, based on ECG (e.g. pathological Q waves) and echocardiography (e.g. regional wall motion abnormalities), was routinely subjected to a stress test, cardiac nuclear imaging, and, if indicated, cardiac catheterization. All laboratory investigations and pharmacology undertaken and prescribed as part of routine clinical management were also recorded in the clinical registry. However, the duration of prescribed medication (including HAART) was not documented.

Human immunodeficiency virus/acquired immunodeficiency syndrome-related cases

It is important to note that HIV testing was only performed when it was clinically indicated and patient consent provided. This report focuses on all cases of heart disease or other form of CVD accompanied by a concurrent diagnosis of HIV/AIDS. Determination of HIV-related cases was made by K.S. and S.S. following independent review and consensus agreement of the classifications presented in

Table 1 Clinical definitions used to classify cases

Study definition	Criteria
LV systolic dysfunction	LVEF $\leq$ 45%
Diastolic dysfunction	Based on *E/A* ratio and deceleration time according to generally accepted criteria[14]
Idiopathic dilated cardiomyopathy	LVEF $\leq$ 45% and possibly LVEDD $>$ 55 mm of indeterminate origin (CAD excluded by coronary angiography)
CAD	Confirmed diagnosis via coronary angiogram; regional wall motion abnormality routinely investigated for CAD
Hypertensive heart failure	Documented blood pressure of $>$180/100 mmHg, accompanied by symptoms of heart failure, increased LV septal thickness ($>$1.3 mm), diastolic dysfunction, and/or LV systolic dysfunction
Pericardial effusion/pericarditis	Documented pericardial effusion $>$0.5 cm. Patients with effusion due to *Mycobacterium tuberculosis* typically have fibrin strains and raised serum adenosine deaminase. Smaller effusions with underlying LV dysfunction were attributed as being due to heart failure. Only a subfraction of the cases underwent pericardiocentesis
Pulmonary arterial hypertension/right heart failure	Isolated pulmonary hypertension (primary) or secondary to diseases such as tuberculosis. Heart failure secondary to right-sided pathology with increased jugular venous pressure and liver size, tricuspid regurgitation, and/or elevated RVSP $\geq$ 35 mmHg. Usually accompanied by peripheral oedema as unique or concomitant to left heart failure
HIV-related cardiomyopathy	Group A: Symptomatic patients (NYHA II–IV) with signs of heart failure with or without concurrent evidence of dilated ventricles with LV systolic dysfunction. More common in advanced immune suppression and independently associated with death Group B: LV dysfunction (including systolic impairment or diastolic dysfunction) in asymptomatic patients undergoing routine echocardiography (subclinical cardiac dysfunction) Group C: Hospitalized patients with WHO Stage IV defining illness who develop heart failure in the absence of prior evidence of heart disease

Table 1 which are integrated with European Society of Cardiology guidelines.[16] A consecutive group of HIV-positive patients presenting with a *de novo* acute coronary syndrome and enrolled into the registry were also recruited into a nested substudy of the clinical presentation, inflammatory markers, and thrombotic profile HIV-related CAD.[17] Coronary angiography and coronary intravascular ultrasound were performed as previously described in this cohort.[18]

Statistical analyses

All study data were documented and entered into the study database by experienced cardiac nurses. Data were then verified and analysed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA) by S.S. and M.J.C. Normally distributed continuous data are presented as the mean $\pm$ standard deviation and non-Gaussian distributed variables as the median plus inter-quartile range (IQR). Percentages are presented with 95% confidence intervals (CIs) where appropriate. Comparisons according to demographic and clinical profile involved χ^2 analysis with calculation of odds ratios (ORs) and 95% CIs for discrete variables. Student's *t*-test and analysis of variance were applied for normally distributed continuous variables and the Mann–Whitney *U*-test for non-normally distributed continuous variables. Multiple logistic regression analyses (entry model) were performed on age, sex, ethnic origin, education status, origin of birth, and baseline risk factors (where appropriate) to derive an adjusted OR. Significance was accepted at the two-sided level of 0.05.

Results

Study cohort

Overall, 518 of 5328 cases (9.7%, 95% CI 9.0–10.6%) with newly diagnosed heart disease or other CVD were identified as HIV-positive; 403 of those cases (7.6%) underwent HIV test at the time of the registry. Of those specifically tested, 170 of 403 (42%) were found to be HIV-positive and underwent counselling for newly diagnosed HIV status. The remaining 348 patients had recorded a positive HIV test at the referral site. The mean age was 40 $\pm$ 14 years. There were more women (320 cases, 62%) and patients of African descent (500 cases, 97%; *Table 2*). Women were on average 4 years younger than men. However, the two most represented age groups in women and men were those aged 20–29 years (35 and 35%, respectively) and 30–39 years (24 and 33%). A large proportion of patients (39%) had little or no education with a similar proportion (38%) originating from Soweto. On presentation, around one-third of patients had LV systolic dysfunction (29%) with minimal sex-based differences. Notably, women had significantly higher body mass indices and were more likely to present with anaemia. The majority of patients (98%) were in sinus rhythm; the remainder comprised six cases of bradycardia/heart block, five cases of atrial fibrillation, and one tachyarrhythmia. Overall, 54% of all HIV/AIDS cases were receiving HAART on clinical presentation.

The clinical presentation of HIV cases differed markedly to the rest of the overall study cohort ($n = 4810$; *Table 2*). On an adjusted basis, the 518 HIV cases were significantly younger (OR 0.95, 95% CI 0.95–0.96 per year; $P < 0.001$), more likely to be of African origin (OR 3.23, 95% CI 1.99–5.23 vs. rest; $P < 0.001$), and received less education (OR 1.35, 95% CI 1.09–1.65 for those with $<$6 years education; $P < 0.001$). More specifically, compared with those 795 cases (51% attributable to rheumatic heart disease) presenting with a communicable form of heart disease (primary diagnosis), those presenting with a primary diagnosis related to HIV (330 cases) were also significantly younger (OR 0.97, 95% CI 0.96–0.98 per year; $P = 0.012$), more likely

Table 2 Clinical and socio-demographic profile of identified human immunodeficiency virus/acquired immunodeficiency syndrome cases

	HIV/AIDS cases vs. rest of Heart of Soweto cohort			Sex-based comparison of HIV/AIDS cases		
	HIV cases ($n = 518$)	Rest ($n = 4810$)	*P*-value	Female ($n = 320$)	Male ($n = 200$)	*P*-value
Demographic profile						
Female	320 (62%)	2850 (59%)	0.258	320 (100%)	—	—
African descent	500 (97%)	4126 (86%)	<0.001	314 (98%)	186 (93%)	0.006
Age (years)	39 ± 13	53 ± 17	<0.001	38 ± 13	42 ± 13	0.002
Born in Soweto	195 (38%)	1730 (36%)	0.470	123 (38%)	72 (36%)	0.636
<6 years education	203 (39%)	2061 (43%)	0.701	116 (36%)	87 (44%)	0.111
Clinical presentation						
Heart rate (b.p.m.)	99 ± 22	84 ± 19	<0.001	100 ± 22	97 ± 21	0.149
SBP (mmHg)	119 ± 22	134 ± 27	<0.001	119 ± 21	117 ± 23	0.826
DBP (mmHg)	72 ± 14	76 ± 15	<0.001	72 ± 14	71 ± 14	0.907
Body mass index (kg/m^2)	24.4 ± 4.3	28.6 ± 7.5	<0.001	25.4 ± 5.9	22.8 ± 3.6	<0.0001
Palpitations	289 (56%)	2513 (52%)	0.292	193 (60%)	96 (48%)	0.008
Median (IQR) eGFR	105 (84–137)	85 (63–108)	<0.001	101 (83–133)	113 (85–140)	0.046
Anaemia	157 (30%)	767 (15%)	<0.001	107 (33%)	50 (25%)	0.018
LVEF (%)	52 ± 16	55 ± 16	0.002	53 ± 16	50 ± 17	0.194
LV systolic dysfunction	148 (29%)	1041 (22%)	0.036	86 (27%)	62 (31%)	0.214
LVEDD (mm)	49 ± 9	47 ± 11	0.334	47 ± 9	51 ± 9	0.001
LVESD (mm)	35 ± 11	34 ± 12	0.209	34 ± 10	37 ± 11	0.154
RVSP ≥ 35 mmHg	51 (9.8%)	393 (8.2%)	0.079	28 (8.8%)	23 (12%)	0.564
NYHA class II, III, or IV	400 (77%)	3245 (67%)	<0.001	249 (78%)	151 (76%)	0.459
Primary diagnosis						
HIV-related CMO	196 (38%)	0 (0%)	<0.001	117 (37%)	79 (40%)	0.329
Pericarditis	65 (13%)	58 (1.2%)	<0.001	36 (11%)	29 (15%)	0.288
Valve disease	58 (11%)	668 (14%)	0.604	43 (13%)	15 (7.5%)	0.045
Hypertension	42 (8.1%)	38 (20%)	<0.001	26 (8.1%)	16 (8.0%)	0.952
Right heart failure	34 (6.6%)	311(6.5%)	0.778	21 (6.6%)	13 (6.5%)	0.963
Cerebrovascular disease	18 (3.5%)	69 (1.4%)	0.002	14 (4.4%)	4 (2.0%)	0.155
Post-partum CMO	17 (3.3%)	105 (2.2%)	0.121	17 (5.3%)	—	—
Coronary artery disease	14 (2.7%)	567 (12%)	<0.001	6 (1.9%)	8 (4.0%)	0.149
Other diagnoses						
Type 2 diabetes	12 (2.3%)	305 (6.3%)	<0.001	8 (2.5%)	4 (2.0%)	0.704
Hypertension	102 (20%)	2104 (44%)	<0.001	58 (18%)	44 (22%)	0.524
Pericarditis	63 (12%)	116 (2.4%)	<0.001	36 (11%)	27 (14%)	0.677

SPB, systolic blood pressure; DBP, diastolic blood pressure; CMO, cardiomyopathy. Pericarditis includes cases of pericardial effusion.

to be of African origin (OR 2.48, 95% CI 1.20–5.15 vs. rest; $P < 0.001$), and more commonly born in Soweto (OR 1.43, 95% CI 1.08–1.88 vs. rest; $P = 0.012$).

Figure 1 shows the overall distribution of primary diagnoses in all 518 HIV-positive cases; the most common being HIV-related cardiomyopathy (38%, 95% CI 34–42%), pericardial effusion/pericarditis (13%, 95% CI 10–16%), valve disease including 32 cases of rheumatic heart disease (11%, 95% CI 9–14%), and right heart failure (7%, 95% CI 4.7–9.0%). The only sex-based difference was a greater proportion of women with a primary diagnosis of valve disease (OR 1.76, 95% CI 1.00–3.08).

Human immunodeficiency virus-related cardiomyopathy

Table 3 shows the demographic and clinical profile of the 196 patients with HIV-related cardiomyopathy. Women (60%) were an average of 6 years younger than men and were more likely to be obese (OR 3.47, 95% CI 1.06–11.5), present with palpitations (OR 1.58, 95% CI 1.21–2.06), and prescribed digoxin (OR 3.50, 95% CI 1.25–9.81). Alternatively, men were more likely to have a history of smoking (OR 8.63, 95% CI 4.45–16.8). At presentation, HIV-related cardiomyopathy cases (64%) were more likely to be prescribed HAART than the rest (127/196 vs. 147/322; OR 2.85, 95% CI 1.81–3.88). When

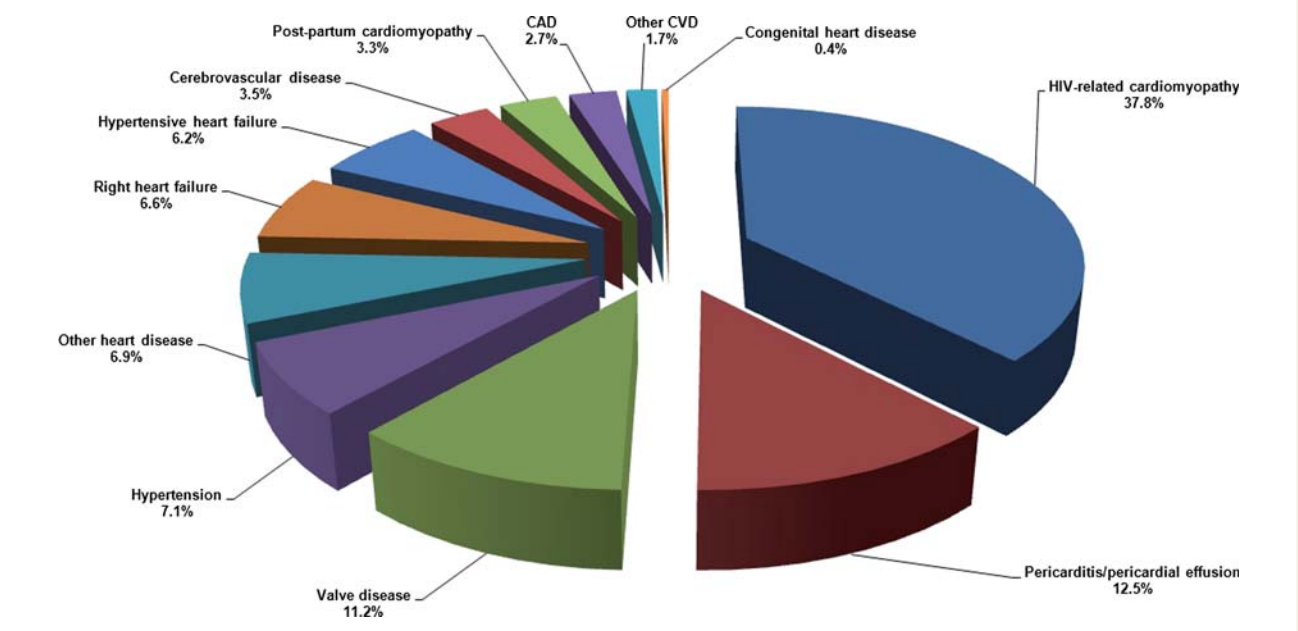

Figure 1 Primary diagnosis of all human immunodeficiency virus-positive cases ($n = 518$).

measured, viral load was significantly higher in HIV-related cardiomyopathy cases [median 110 000 (IQR 26 000–510 000) vs. 19 000 (IQR 3200–87 000); $P = 0.018$] and their CD4 count was lower [median 180 (IQR 71–315) vs. 211 (96–391); $P = 0.019$]. However, there was no difference in respect to haemoglobin, platelets, white cell count, and sodium and creatinine levels (data not shown). Human immunodeficiency virus-related cardiomyopathy cases prescribed HAART therapy had a lower mean CD4 count (159 ± 19.4 vs. 224 ± 38.6; $P = 0.035$).

Table 4 shows the pattern of HIV-related cardiomyopathy according to the pre-specified subgroups in those of African descent ($n = 193$). The largest subgroup (51%) was those with dilated ventricles and LV dysfunction (*Group A*), 47 patients (24%) had asymptomatic LV dysfunction (*Group B*), and the same number (24%) presented with severe forms of cardiomyopathy associated with advanced immunosuppression (WHO Stage IV AIDS defining illnesses), who developed heart failure in the absence of prior evidence of cardiac disease (*Group C*).

Pericardial disease

A primary and secondary diagnosis of pericardial effusion/pericarditis was diagnosed in 65 (13%) and 63 (12%) cases, respectively. Combined, these cases represented 2.4% (95% CI 2.0–2.8%) of all *de novo* presentations of heart disease in the wider cohort. None of these cases were prescribed HAART. Large (<2.5 cm), medium (1–2.5 cm), and small (<1 cm) pericardial effusions requiring cardiocentesis were found 17, 18, and 9 and 13, 45, and 62%, respectively, in those with a primary or secondary diagnosis.

Human immunodeficiency virus-related pulmonary arterial hypertension

In total, 31 women and 11 men presented with HIV-related pulmonary arterial hypertension (8.1%, 95% 6.1–10.8%). Women were significantly younger than men (39 ± 14 vs. 51 ± 18 years; $P < 0.0001$). There were no differences in any clinical parameters according to the presence or absence of anti-retroviral therapy.

Coronary artery disease

Of 581 *de novo* cases of CAD in the Heart of Soweto cohort, a total of 14 patients (2.4%, 95% CI 1.5–4.0%) with a mean age of 41 ± 13 years were HIV-positive. Of these, 13 were of African origin and 8 were males. All presented with an acute myocardial infarction (AMI). The mean viral load was 4769 ± 3109 with a CD4 count of 298 ± 184. Coronary intravascular ultrasound typically demonstrated a fresh thrombus with no or minimal underlying atherosclerotic disease. There were no differences in any clinical parameters according to the presence or absence of HAART.

Discussion

This is the largest, integrated study of the spectrum of cardiac manifestations of HIV/AIDS relative to the overall pattern of *de novo* presentations of advanced heart disease in sub-Saharan Africa. With a high prevalence of sero-positive individuals and a historical lack of HAART, combined with epidemiological transition towards non-communicable forms of heart disease,[7,8] the geographically distinct enclave of Soweto represents an important barometer of the current and future impact of HIV/AIDS on the heart health of urban Africans. Importantly, two forms of heart disease commonly linked to HIV/AIDS in previous studies,[5] HIV-related cardiomyopathy (3.7% of the entire cohort) and pericardial disease as primary and secondary diagnosis (2.4%) while representing a large component of identified HIV/AIDS-related cases, were only minor contributors to the overall burden of heart disease reflected in the overall *Heart of Soweto* cohort of

Table 3 Pattern of human immunodeficiency virus-related dilated cardiomyopathy in men and women (n = 196)

	All (n = 196)	Sex-based comparisons		
		Females (n = 117)	Males (n = 79)	P-value
Demographic profile				
Females (%)	117 (60%)	117 (100%)	—	—
African descent	193 (99%)	115 (99%)	78 (99%)	0.804
Age (years)	41 ± 13	39 ± 13	45 ± 13	0.005
<6 years education	78 (40%)	41 (35%)	37 (47%)	0.098
Born in Soweto	80 (41%)	49 (42%)	31 (39%)	0.712
Clinical presentation				
Smoker	94 (48%)	33 (28%)	61 (77%)	<0.0001
Obese (BMI > 30 kg/m^2)	18 (9.2%)	15 (13%)	3 (3.8%)	0.024
Heart rate (b.p.m.)	102 ± 21	104 ± 23	100 ± 18	0.230
SBP (mmHg)	115 ± 20	115 ± 19	115 ± 21	0.970
DBP (mmHg)	71 ± 14	71 ± 15	73 ± 14	0.534
Palpitations	120 (61%)	84 (72%)	36 (46%)	<0.0001
Median (IQR) eGFR	99 (76–133)	97 (76–128)	102 (76–140)	0.274
Anaemia	57 (29%)	36 (31%)	21 (27%)	0.234
LVEF (%)	46 ± 17	47 ± 17	43 ± 17	0.101
LV systolic dysfunction	119 (61%)	66 (56%)	53 (67%)	0.122
LV diastolic dysfunction	116 (59%)	64 (55%)	52 (66%)	0.125
LVEDD (mm)	51 ± 9.2	49 ± 8.7	54 ± 8.4	0.024
LVESD (mm)	39 ± 12	37 ± 11	40 ± 11	0.104
Right heart failure	35 (18%)	24 (21%)	11 (14%)	0.237
NYHA class II, III, or IV	168 (86%)	102 (87%)	66 (84%)	0.914
Other diagnosis/complications				
Cerebrovascular disease	5 (2.6%)	3 (2.6%)	2 (2.5%)	1.000
Type 2 diabetes	6 (3.1%)	3 (2.6%)	3 (3.8%)	0.270
Hypertension	34 (17%)	18 (15%)	16 (20%)	0.296
Pericardial effusion/pericarditis	31 (16%)	18 (15%)	13 (17%)	0.873
Right heart failure	35 (18%)	24 (21%)	11 (14%)	0.237
Valve dysfunction	62 (32%)	32 (27%)	30 (38%)	0.235
Prescribed treatment				
Diuretic (loop/thiazide)	99 (51%)	59 (50%)	40 (51%)	1.000
Spironolactone	69 (35%)	39 (33%)	30 (38%)	0.542
β-Blocker	57 (29%)	35 (30%)	22 (28%)	0.701
ACE-inhibitor	51 (26%)	30 (26%)	21 (27%)	0.894
Aspirin or warfarin	29 (15%)	13 (11%)	16 (20%)	0.105
Digoxin	24 (12%)	20 (17%)	4 (5.1%)	0.009

SPB, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

5328 *de novo* case presentations.[7,8] Moreover, those with HIV-related pulmonary arterial hypertension and CAD plus HIV-positive status represented only 0.8 and 0.3% of cases, respectively. Other cases attributable to HIV/AIDS were many and varied. Given an estimated 5.5 million people infected, 500 000 HIV-related deaths annually, and previous reports suggesting high levels (up to 1 in 2 affected cases) of myocardial and/or pericardial disease[5] in South Africa, these data are encouraging. The expected 'tsunami' of cardiac cases from the HIV pandemic, for the moment, has yet to arrive. With the introduction of HAART and pre-warning of its potential impact on premature forms of CAD, there is still potential to truncate at least one of the many devastating consequences of this disease.

Consistent with previous reports, the most common diagnosis in HIV-positive cases was HIV-related cardiomyopathy; a late stage manifestation of HIV infection and a trigger for HAART independent of the CD4 count.[19,20] Its aetiology and pathogenesis is largely unknown, with multiple factors seeming to affect myocardial tissue: (i) direct HIV infection of the myocardial cells (CD4-independent infection though glycoprotein 120 and Tat protein), (ii) infection with other pathogens (e.g. toxoplasma gondii, Coxackie Virus, and Parvo B19), (iii) autoimmune reactions

Table 4 Clinical distribution of human immunodeficiency virus-related cardiomyopathy in African patients (n = 193)

	Group A (n = 99)	Group B (n = 47)	Group C (n = 47)	All (n = 193)
Women	50 (51%)	36 (77%)	29 (62%)	115 (60%)
Age (years)	40 ± 15	43 ± 12	39 ± 11	41 ± 13
<6 years education	34 (34%)	23 (49%)	23 (49%)	80 (42%)
Originally from Soweto	39 (39%)	20 (43%)	18 (38%)	77 (40%)
Clinical presentation				
Heart rate (b.p.m.)	104 ± 20	97 ± 22	102 ± 20	102 ± 21
SBP (mmHg)	113 ± 20	117 ± 21	122 ± 22	116 ± 21
DBP (mmHg)	71 ± 14	72 ± 16	73 ± 16	72 ± 15
NYHA class II, III, or IV	84 (85%)	41 (87%)	41 (87%)	166 (86%)
Peripheral oedema	54 (55%)	20 (43%)	28 (60%)	102 (53%)
Raised jugular venous pressure	4 (4.0%)	5 (11%)	8 (17%)	17 (9%)
Palpitations	59 (60%)	29 (62%)	29 (62%)	117 (61%)
Median (IQR) eGFR	106 (68–138)	99 (65–129)	101 (67–142)	103 (67–134)
Anaemia	32 (32%)	11 (23%)	13 (28%)	56 (29%)
LVEF (%)	45 ± 16	40 ± 17	42 ± 16	43 ± 16
LV systolic dysfunction	53 (54%)	31 (66%)	32 (68%)	116 (60%)
LV diastolic dysfunction	46 (46%)	10 (21%)	13 (28%)	69 (36%)
LVEDD (mm)	52 ± 8	51 ± 10	51 ± 9	52 ± 9
LVESD (mm)	41 ± 11	37 ± 12	35 ± 11	39 ± 12
RVSP ≥ 35 mmHg	21 (21%)	11 (23%)	11 (23%)	43 (22%)
Prescribed treatment				
Loop/thiazide diuretic	53 (54%)	25 (53%)	18 (9%)	96 (50%)
Spironolactone	38 (39%)	16 (34%)	14 (7%)	68 (35%)
ACE-inhibitor	37 (51%)	13 (28%)	8 (17%)	58 (30%)
β-Blocker	33 (33%)	16 (34%)	7 (15%)	56 (29%)
Digoxin	12 (12%)	5 (11%)	7 (15%)	24 (12%)

Groups A, B, and C defined as per study definition in *Table 1*. SPB, systolic blood pressure; DBP, diastolic blood pressure.

(e.g. antibodies against alpha myosin), (iv) drug abuse and drug toxicity, (v) malnutrition, and (vi) endocrine dysfunction.[21–23] Its incidence has significantly decreased following the introduction of HAART in developed countries.[24] Therefore, our observation of more patients being on HAART at the time of diagnosis should be interpreted with caution. The immune reconstitution inflammatory syndrome has been described in most organ systems[25] including the heart,[26] and, potentially, there was a higher than usual prevalence of cardiac involvement in this paradoxical immune reaction in this population. Alternatively, these data may reflect increased detection of the condition in those diagnosed as HIV-positive. None of anti-retroviral agents recommended for use in South Africa have been shown to cause cardiomyopathy in large cohort studies.[27] Only 12.5% of all HIV-positive cases presented with clinically significant pericardial effusion/pericarditis. Previous studies suggest that pericardial effusion is the most common symptomatic and asymptomatic cardiac manifestation of HIV in Africa.[5] These results, from a more peri-urban environment, provide a slightly different picture, but may reflect the fact that the routine management of tuberculosis (including cardiac manifestations) is not routinely undertaken by cardiologists.

A key focus has been the link between HIV/AIDS, its treatment, and the development of premature forms of CAD. Human immunodeficiency virus infection may independently predispose to AMI via a combination of endothelial dysfunction, a heightened pro-inflammatory state, dyslipidaemia, and thrombosis.[5,28–30] Similarly, protease inhibitor therapy has the potential to induce an adverse metabolic phenotype that involves a similar pathological response that increases the risk of AMI (particularly during prolonged treatment). There are few data describing CAD in HIV patients not receiving HAART. This is problematic, considering that this represents the majority of patients in sub-Saharan Africa. We recently showed that HIV-positive patients of African origin not prescribed HAART and presenting with AMI are younger with fewer traditional risk factors, having less atherosclerosis but higher thrombotic burden on angiography, suggesting a hypercoagulable state.[2] We further showed evidence of thrombophilia with lower protein C levels and higher Factor VIII levels compared with HIV-negative patients.[17] Furthermore, patients not on HAART have evidence of a pro-inflammatory state accompanied by elevated markers of endothelial activation, suggesting an aetiopathogenic link between HIV, inflammation, and thrombosis in this

traditionally low-risk population.[18] The exact pathogenic role of HIV, independent of associated modifiable and non-modifiable risk factors, is difficult to determine but may be important as a contributory factor in an already 'vulnerable' patient.

Our study has a number of limitations. First, our clinical registry was not specifically designed to study the prevalence of HIV/AIDS; our main aim was to examine the impact of AIDS on the burden of *de novo* presentations of heart disease in this community. For example, we do not have data on the duration of HAART on presentation. This study cohort only reflects those who seek specialist care at the hospital (i.e. more advanced presentations). Moreover, we did not systematically validate diagnostic data nor seek definitive HIV status in every case (a contentious issue in South Africa). Importantly, however, more definitive investigation of HIV status occurred when clinically indicated.

Overall, these data capture the status of the HIV pandemic and related manifestations of cardiac disease in South Africa in the present time; the government having recently initiated a nationwide implementation of HAART. Hopefully, this will have a mitigating effect on presentations of HIV-related cardiomyopathy and pericardial effusion/pericarditis. Ongoing surveillance is required to document and respond to the impact of HAART on dyslipidaemia and CAD in a society with historically low levels of the same. Moreover, our findings reinforce that data from the developed world cannot be readily extrapolated to Africa. Overall, we found that CAD due to HIV/AIDS remains rare compared with cases of HIV-related cardiomyopathy and that the latter represented only a small proportion of *de novo* cardiac presentations. Overall, these data have important clinical and public health implications for Sub-Saharan Africa, the wider African continent, and other parts of the world in epidemiological transition where a confluence of non-communicable and infective disease arises.

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