ORIGINAL ARTICLE

Prevalence of subclinical Cardiovascular Disease in healthy HIV infected patients at the University Teaching Hospital in Lusaka, Zambia

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ABSTRACT

Background: Cardiovascular diseases are among the leading cause of morbidity and mortality worldwide. The association between HIV and CVD has been established in many studies. However, information is still lacking on subclinical disease as well as its associated risk factors in this population. This study aimed at establishing the prevalence of subclinical CVD among clinically healthy HIV people attending their regular out- patient visits. It also looked at risk factors (traditional and non traditional) as well as the association of CVD to the CD4 count.

Methods: we enrolled a total of 243 asymptomatic HIV-infected patients from the HIV outpatient clinic at the University Teaching Hospital. Data collected included demographic characteristics, duration of HIV infection, drug history including HAART regimen and cardiovascular risk factors (hypertension, diabetes and smoking). Clinical data included blood pressure, weight and height. Laboratory data included CD4 counts, serum creatinine, total cholesterol and triglycerides. We tested for subclinical CVD using 3 tools: Ankle Brachial Index (ABI) to measure for the presence of peripheral artery disease, 12 lead Electrocardiogram (ECG) for electrical abnormalities and transthoracic Echocardiography (ECHO), to measure abnormalities in cardiac structure and function. At analysis, patients where dichotomised into those with CD4≤350 and those with CD4>350.

Results: participants characteristics were as follows: the mean age, 42 years (SD±10); 143 (58.5%) females; CD4≤ 350cells/ml was found in 140 (57.6%); 112(86.2%) were receiving HAART with 86.2% being on 1st line regimen. Systolic hypertension was present in 84(34.6%), diastolic hypertension in 89(36.6%) and 39.5% had creatinine clearance<90. Diabetes and current smoking were not very common (3.3% and 2.9% respectively). High total cholesterol was found in 19(7.82%) of the participants while 37(15.23%) had high triglycerides. On ECG, ECHO and ABI, abnormalities were found in 53.9%, 44.4% and 20.2% respectively). The commonest cardiac lesion on both ECG and ECHO was left ventricular hypertrophy (27.4% and 23.3% respectively). Participants with CD4≤350 had higher prevalence of abnormalities on ECG (P=0.022) and ABI (P=0.043). Clinical factors associated with increased risk of subclinical CVD on multivariate logistical regression included CD4≤350, systolic BP>140mmHg and diastolic BP>90mmHg.

Conclusions*:* Prevalence of subclinical CVD in healthy HIV infected patients is high and those with CD4≤350 have a higher risk. Hypertension is the most important traditional CVD risk factor in this population. There is need to screen HIV patients attending their routine clinic visits for hypertension and subclinical CVD. ABI and ECG are readily available in most institutions and can be used with minimal expertise.

INTRODUCTION

The burden of cardiovascular diseases (CVDs) in the world is enormous and growing, and the majority of those affected are in developing countries.[1] In 2002 it was estimated that 29% of deaths worldwide (16.7 million deaths) were due to CVD and that 43% of global morbidity and mortality, measured in disability-adjusted life years (DALYs), was caused by CVD.[2]

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In most African countries CVD is now the second most common cause of death after infectious disease, accounting for 11% of total deaths.[3] Projections from the Global Burden of Disease Project suggest that from 1990 to 2020, the burden of CVD faced by African countries will double. A large proportion of the victims of CVD will be middle-aged people. The poor will suffer disproportionately as a consequence of their higher disease risk and limited access to health care.[4]

The association of HIV infection and cardiac pathology was recognised in the early stages of the epidemic. Most studies were carried out in Europe and North America; these studies indicate that HIV infection is commonly associated with cardiac abnormalities.[5,6,7] Studies published over the past 3 years have tracked the incidence and course of HIV infection in relation to cardiac illness in both children and adults.[8] These studies show that sub-clinical echocardiographic abnormalities independently predict adverse outcomes in terms of morbidity and mortality and identify high-risk groups to target for early intervention and therapy.[8]

In Africa, the incidence of AIDS-related cardiac disease is very high compared to that seen in western developed countries. For instance, in the period from 1993 to 1999 in Burkina Faso, 79% of the AIDS patients exhibited heart involvement, Zimbabwe found a prevalence of 50% among acutely ill hospitalised patients, in DRC the prevalence was 55%, [9] whereas in an Italian study in the period from 1992 to 1995, the incidence of AIDS-related cardiac disease was 6.5%.[10,11] The trend remained similar in many other studies done in Africa.

However, to date, the prevalence of cardiovascular disease among Zambian HIV infected patients remains unknown despite several cases of end stage cardiac disease being encountered on a daily basis.[12] At the moment, HIV programs are focused primarily on support of active campaigns to get universal access to combinational ART. As a result, most forms of sub-clinical cardiovascular diseases are missed in their early stages resulting in patients presenting with advanced disease, which has very high morbidity and mortality.[13] Studies show that the incidence of heart failure in patients with subclinical cardiac dysfunction may be as high as 30%.[13]

METHODOLOGY

Study design

This was a descriptive cross sectional study

Study setting and population

The study was carried out in the adult infectious diseases centre in UTH, which is an outpatient HIV clinic. The study population included clinically healthy HIV infected patients who were coming for their regular scheduled clinic visits. All the participants were over 18 years of age and had signed informed consent. We excluded those with documented cardiac disease, woody edema of the limbs, or amputation of any limb as this would have made it difficult to measure the ankle brachial index.

Clinical procedure

Patients were recruited during working hours on a daily basis in AIDC. Screening was done in line with exclusion criteria. A detailed history was taken by research staff at recruitment. Information gathered included patient demographics, duration of illness from time of diagnosis, type of ART being taken and duration. Other drugs being taken were also documented. Participants were asked on the presence of any CVD risk factors namely; diabetes, hypertension and tobacco smoking. A physical examination was conducted, including measurements of BP, pulse, weight and height; cardiac auscultatory findings were documented. We collected blood samples for total cholesterol, triglycerides, CD4 counts and serum creatinine.

Each patient then underwent ECG, ECHO and Ankle Brachial Index (ABI) measurements. We recorded a standard 12 lead ECG calibrated at 10 mm, with a speed of 25mm/sec. Limb lead II was used as the rhythm strip.

ECHO measurements were done with the participant placed in the left lateral position; Left ventricular systolic function was measured from the left parasternal long axis or short axis views using the Teicholz method in M-Mode; any abnormal result was verified using the 2-dimensional Simpsons biplane method in the 4 chamber apical view. Chamber sizes and wall thicknesses were measured in 2 dimensional mode. Pulsed wave, continuous wave and colour flow Doppler studies were used in determining flow velocities and pressures across the mitral valve, left ventricular outflow tract (LVOT), aortic valve, tricuspid and pulmonic valves. The pericardium and the Inferior vena cava were assessed from the subcostal view.

Blood pressure measurements to obtain ABI readings were done in all the four limbs. We ensured that the legs were kept warm with a blanket to avoid erroneously obtaining low readings as a result of cold-induced vasoconstriction.

STUDY DEFINITIONS

The following study definitions were used

Subclinical Cardiovascular disease – defined as any abnormality identified on ECG, ECHO or ABI, that has not been documented before and the participant shows no symptoms despite the abnormality.

Abnormal ECG [14]

According to the Minnesota code for interpretation of ECG abnormalities, an abnormal ECG was defined by the presence of the following; left ventricular hypertrophy, arrhythmias, AV conduction defects, ventricular conduction defects, QT prolongation, ST-T changes, p wave abnormalities, abnormal Q waves and abnormal axis deviation.

Abnormal ECHO[17,19]

Using recommendations by the American Society of Echocardiography and European Association of cardiovascular imaging, an abnormal echo was defined by the presence of the following

- Left ventricular systolic dysfunction – ejection fraction less than 52% for males and less than 54% for females
- Left ventricular diastolic dysfunction – abnormalities in the e/a ratio, with e/a<0.8 for impaired relaxation, e/a = 0.8-1.9 for pseudonormal pattern (abnormality unmasked using the vasalva manoeuvre and e/a≥2 for restrictive pattern.
- Left ventricular dilatation (mid cavity diameter at end diastole) - ≥54mm for females and ≥60mm for males
- Left atrial dilatation (diameter) - ≥39mm in females and 40mm in males
- Right atrial dilatation (minor axis) - ≥45 mm for both sexes
- Right ventricular dilatation (basal diameter) - ≥42mm for both sexes
- Right ventricular systolic dysfunction (TAPSE) - ≤17mm for both sexes
- Abnormal Pulmonary valve acceleration time (PVAT) - <100ms
- Presence of pericardial effusion – defined as an echo-free space of >10mm.

Valvular abnormalities in terms of structure and function were defined using standard Doppler measurements.

Abnormal ABI

This was calculated as a ratio of the systolic BP at the ankle (dorsalis pedis artery) to the systolic BP at the arm (brachial artery). A value of <0.9 defined an abnormal ABI[20]

Traditional CVD risk factors[21] – Using data from the Framingham heart study, CVD risk factors were defined as presence of hypertension, diabetes, smoking, and abnormal lipids.

Non traditional CVD risk factors – these were defined as risk factors specific to HIV infected patients that have been shown to increase risk of future CVD events. These were: presence of kidney dysfunction, duration of HIV infection, exposure to protease inhibitors, CD4 count ≤ 350cells/ml, using data obtained from various studies.[6, 10,16,18]

STUDY OUTCOMES

Our primary outcome was evidence of subclinical cardiovascular disease on ECG, ECHO or ABI measurements; secondary outcomes included the association between CD4 count and presence of subclinical CVD, prevalence of CVD risk factors (both traditional and non traditional) and the commonest cardiac lesion in our study population.

DATA ANALYSIS

All statistical analysis was done using Epi info version 7. Continuous variables with a Gaussian distribution pattern were expressed as means and standard deviation. A student t-test was used to compare the means. Non-Gaussian type of data was expressed as medians and comparisons were made using the Mann-Whitney U (Kruskal Wallis) test. Categorical variables were expressed as percentages and a Chi square test was used to analyse dichotomous variables.

Cardiovascular outcomes of interest were re-defined as dichotomised categorical variables where "normal" was evaluated against other categories. To determine the association of CD4 count to cardiovascular abnormalities of interest, we dichotomised the variable as CD4≤350 and CD4>350, using data from previous studies. Other continuous variables that were also dichotomised included blood pressure, creatinine clearance, total cholesterol and triglycrides. Multivariate logistic regression models were constructed to determine the association between various clinical factors (e.g. hypertension, CD4 count, HIV duration etc) with the CVD outcomes of interest (abnormal EGC, ECHO and

ABI), and we used the backward elimination method to derive the final adjusted odds ratio starting with variables with the highest p values. A p-value of less than or equal to 0.05 was considered statistically significant.

RESULTS

From April 2014 to October 2014, 250 asymptomatic HIV infected patients were recruited into the study. Of these, 4 were excluded for absconding ECHO exam, whilst 2 refused to have an ECG done and 1 participant had woody hard Kaposi Sarcoma in the right leg. A total of 243 patients had all the data required for analysis. Of these 129(53.1%) had CD4≤ 350cells/ml (see fig 1)

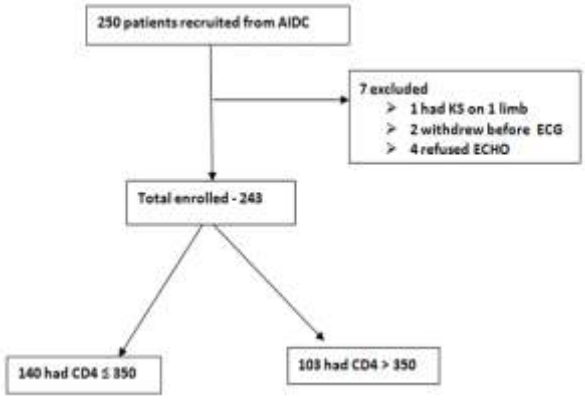

Fig. 1 study participants

5.2 Baseline characteristics of the participants

The baseline characteristics of the participants are shown in table 1. The mean age was 42 years, with age range of 18-86 years and the majority were females. The average CD4 count was 365.5cells/ml. About 90% of the participants were receiving HAART and of these, about 80% were on were on 1st line ART.

Approximately 30% of the participants had HIV for longer than 5 years. On history, hypertension was the commonest traditional CVD risk factor and on clinical examination, this increased two fold for both systolic and diastolic hypertension. On the other hand smoking and diabetes were found in less than 10% of this population. The median BMI was within the normal range. About 40% of these patients exhibited laboratory evidence of kidney dysfunction (CrCl<90). Lipid derangements were also observed with more participants having abnormal triglycerides than total cholesterol.

Table 1: Baseline characteristics of the participants

Characteristic	Participants n=243	Percentage
Age in years –mean (SD)	42.4	±10.60*
No. of females	143	58.53
Duration since HIV diagnosis > 5 yea	80	32.92
Receiving HAART	218	89.71
Regimen: 1st Line	193	79.42
2nd line	22	9.05
3rd line	3	1.23
Diagnosed Hypertension	38	15.64
Diagnosed Diabetic	8	3.29
Current smoker	7	2.88
BMI median (IQR)	23.5	20.8-27.7**
Systolic BP median (IQR)	131	119-149
Systolic BP ≥140mmHg	84	34.57
Diastolic BP median(IQR)	83	74-93**
Diastolic BP≥90mmHg	89	36.63
CD4 count mean(SD)	355.1	±199.9*
CD4 ≤350	140	57.6
Creatinine median(IQR)	75	61-90**
CrCl<90	96	39.51
CKD STAGE: Stage 1	145	59.67
Stage 2	77	31.69
Stage 3	15	6.17
Stage 4	5	2.06
Stage 5	1	0.41
High cholesterol	19	7.82
High triglycerides	37	15.23

**standard deviation, **interquartile range*

Abnormalities on ECG

Figure 3 gives a visual representation of the distribution of various abnormalities seen on ECG in this population.

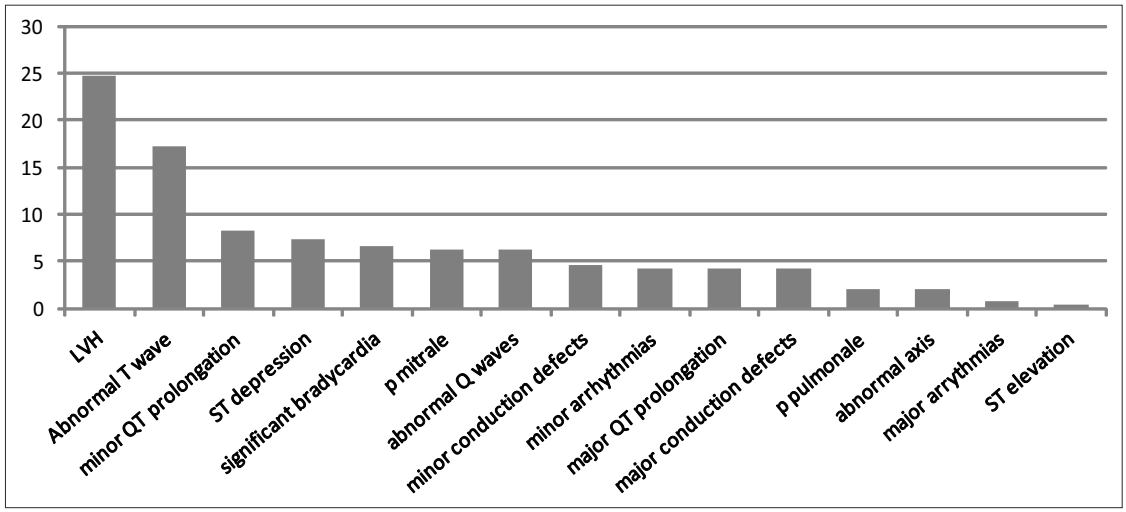

Fig. 3 – abnormalities on ECG

Left ventricular hypertrophy (LVH) was the commonest abnormality seen, followed by abnormal T waves. Other abnormalities included arrthythmias (atrial flutter, atrial fibrillation, premature atrial and ventricular conduction), conduction defects (heart blocks of various degrees), bradycardia, ST –T changes, abnormal Q waves and QT prolongation.

ECG abnormalities and relation to CD4 count

Table 2 shows how the various ECG abnormalities related to the CD4 count. Approximately half of the participants had an abnormal ECG, with more than half having major abnormalities such as major arrhythmias (atrial flutter, atrial fibrillation), atrial and ventricular conduction defects, left ventricular hypertrophy (LVH), and major QT prolongation. Regarding the CD4 count, there was a significant difference in the prevalence of total ECG abnormalities between the 2 groups, with participants with CD4≤350 having a significantly higher prevalence. On the individual abnormalities only LVH and bradycardia were significant for CD4≤350. However, participants with CD4>350 had significantly higher prevalence of QT prolongation, arrhythmias and conduction defects, though the overall numbers were small. The remaining abnormalities were comparable between the two groups.

Table 2 – ECG abnormalities in relation to CD4 count

PARAMETER N (%)	Total n(%) =243(100)	CD4≤350 n=140 (57.6%)	CD4> 350 n=103(42.4%)	P value
ABNORMAL ECG	**131(53.91)**	**82 (58.57)**	**49(47.57)**	**0.045***
MAJOR ABNORMALITIES	79(32.51)	45(32.14)	34(33.01)	0.443
Major arrhythmias	2 (0.82)	1 (0.71)	1 (0.97)	0.424
Major conduction defects	5 (2.06)	1 (0.71)	4 (3.88)	0.060
Abnormal Q waves	15(6.17)	9(6.98)	6(5.26)	0.298
ST elevation	1(0.41)	1(0.78)	0(0.00)	0.531
Left ventricular hypertrophy	**60(24.69)**	**37(28.68)**	**23(20.18)**	**0.027***
Major QT prolongation (>116%)	10(4.21)	3(2.33)	7(6.14)	0.077
MINOR ABNORMALITIES	52(21.4)	43 (33.33)	19 (18.45)	0.171
Significant Bradycardia	16(6.58)	14(10.85)	2(1.78)	**0.002***
Abnormal axis	5(2.06)	2(1.55)	3(2.63)	0.442
ST Depression	18(7.41)	11(8.53)	7(6.14)	0.186
Minor arrhythmias	**10 (4.21)**	**3 (2.41)**	**7 (6.80)**	**0.043***
Minor conduction defects	**11 (4.53)**	**3 (2.14)**	**7 (7.77)**	**0.023***
Abnormal T wave	42(17.28)	23(17.83)	19(16.67)	0.407
Minor QT prolongation (>112%)	20(8.23)	7(5.43)	13(11.40)	**0.049***
P mitrale	15(6.20)	11(7.86)	4(3.92)	0.112
P pulmonale	5(2.07)	3(2.33)	2(1.77)	0.562

*statistically significant

Figure 4. Gives a visual representation of the different ECG abnormalities between the two categories of participants.

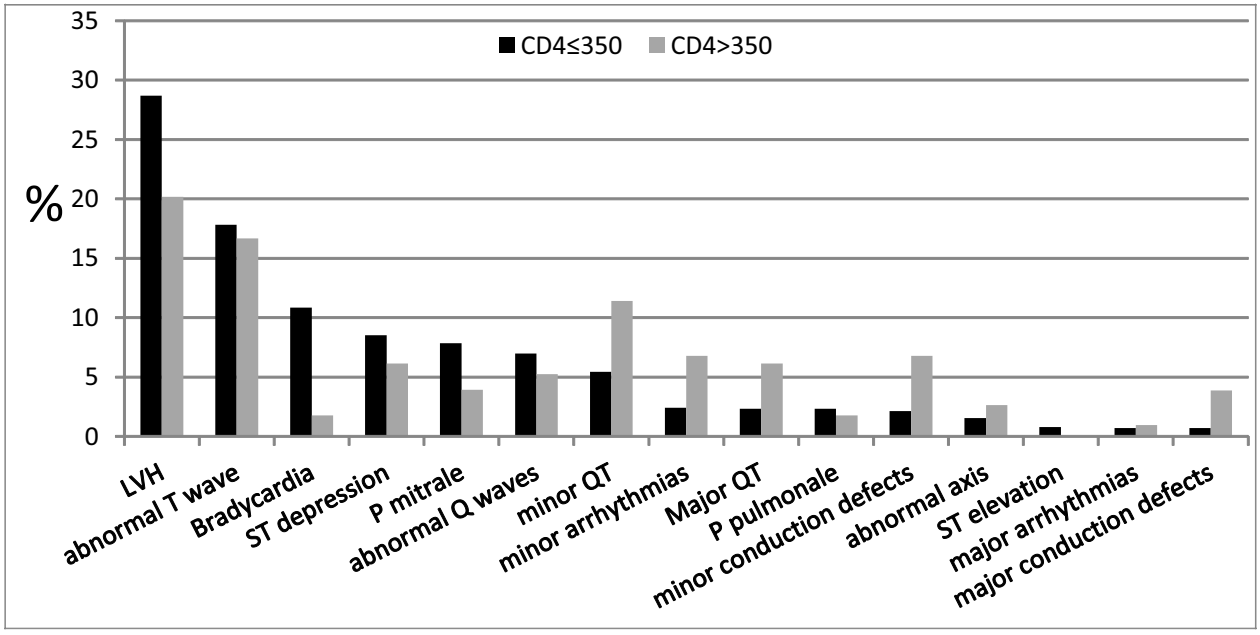

Fig. 4 – ECG abnormalities in relation to CD4 count

5.4 ABNORMALITIES ON ECHO

The distribution of ECHO abnormalities is depicted in figure 5. Once again, left ventricular hypertrophy (LVH) was the commonest ECHO abnormality in this population, followed by left ventricular diastolic dysfunction. Left ventricular systolic function was not so common.

Valvular abnormalities observed in this population were mainly functional in nature, meaning overall valvular anatomy was normal. Right ventricular failure, pulmonary hypertension and pericardial effusion were observed in less than 5% of the participants.

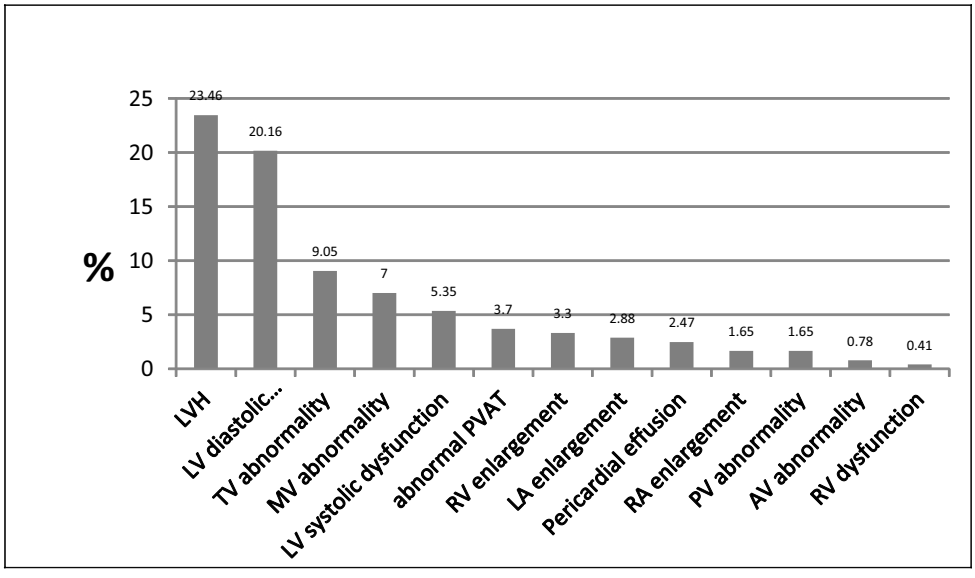

Fig.5 – abnormalities on ECHO

5.4.1- ECHO abnormalities and relation to the CD4 count

Table 3 depicts the various abnormalities seen on echo in relation to the CD4 count. An abnormal ECHO was present in about 45% of the participants, and showed no significant association with CD4≤350 count. However, on the individual abnormalities, participants with CD4 counts ≤350cells/ml had significantly higher prevalence of left ventricular hypertrophy compared to their counterparts. The rest of the parameters were comparable between the two groups.

Table 3 – ECHO abnormalities

PARAMETER	Total n=243	CD4≤350 n=140 (57.6%)	CD4> 350 n=103(42.4%)	P value
Abnormal ECHO	108(44.44)	57(44.19)	51(44.74)	0.465
LV systolic dysfunction	13(5.35)	8(6.20)	5(4.39)	0.275
LV diastolic dysfunction	49(20.16)	22(17.05)	27(23.68)	0.102
LVH	**57(23.46)**	**36(27.91)**	**21(18.42)**	**0.042***
LA enlargement	7(2.88)	3(2.33)	4(3.51)	0.308
RA enlargement	4(1.65)	2(1.55)	2(1.75)	0.268
RV enlargement	8(3.290	3(2.33)	5(4.39)	0.641
RV dysfunction	1(0.41)	1(0.88)	0(0.00)	0.470
MV abnormality	17(7.00)	11(8.53)	6(5.26)	0.167
AV abnormality	3(1.23)	1(0.78)	2(1.75)	0.278
TV abnormality	22(9.05)	15(11.63)	7(6.14)	0.070
PV abnormalities	4(1.65)	3(2.33)	19(9.88)	0.359
Abnormal PVAT	9(3.70)	5(3.88)	4(3.51)	0.446
Pericardial effusion	6(2.47)	3(2.33)	3(2.63)	0.442

***Statistically significant**

Figure 6 is a visual representation of ECHO abnormalities in relation to the CD4 count.

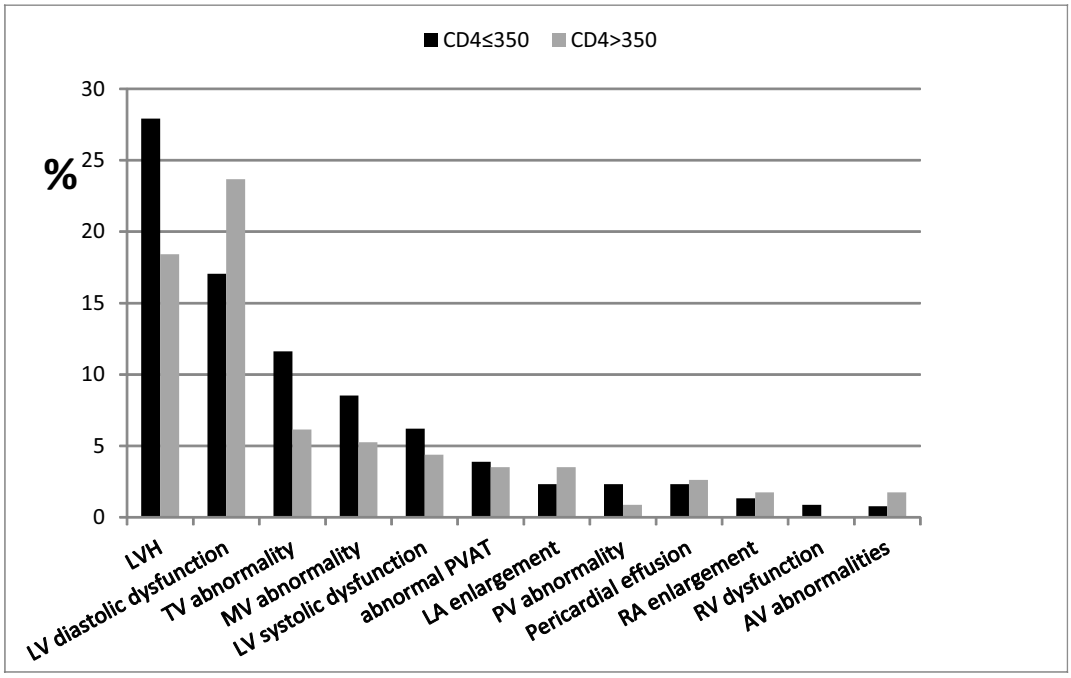

fig.6 -ECHO abnormalities and CD4 count

5.5 Abnormal ABI

Peripheral artery disease as defined by the presence of an abnormal ABI was present in a quarter of the participants (table 4). The majority of those affected showed unilateral limb involvement.

However, in relation to the CD4 count, participants with low CD4 counts had a significantly higher prevalence of peripheral artery disease and had more bilateral limb involvement compared with their counterparts with higher CD4 counts.

Table 4 – Abnormal ABI in relation to CD4 count

PARAMETER	Total n(%)=243(100)	CD4≤350 n=140 (57.6%)	CD4> 350 n=103(42.4%)	P value
Abnormal ABI	49(20.16)	31(24.03)	18(15.79)	0.043*
Limb involvement				
Unilateral	33(13.58)	16(12.40)	17(14.91)	0.287
Bilateral	17(7.00)	15(11.63)	2(1.75)	0.001*

*statistically significant

Clinical correlates of subclinical CVD on logistic regression

On multivariate logistic regression, clinical factors significantly associated with an increased risk of abnormalities on ECG, ECHO and ABI are shown in table 4.

Table 5– clinical correlates of subclinical CVD

	PARAMETER	Crude O.R	C.I	Adjusted O.R	C.I
ABNORMAL ABI	CD4 ≤350cells/ml	**2.20**	**1.12 – 4.34$^{\alpha}$**	**2.18**	**1.09 – 4.33$^{\alpha}$**
	Systolic BP≥140	1.67	0.88 - 3.13	2.00	0.87 - 4.50
	Diastolic BP≥ 90	1.08	0.57 - 2.05	0.70	0.81 - 1.55
	Smoker	1.57	0.29 - 8.34	1.61	0.27 - 9.95
	Diabetic	0.54	0.54 - 4.51	0.45	0.17 - 4.51
	Abnormal lipids	1.19	0.86 - 2.84	1.08	0.51 – 2.40
	HIV diagnosis ≥5yrs	1.06	0.55 - 2.05	0.91	0.45 - 1.93
	Exposure to PIs	1.02	0.36 - 2.87	0.94	0.48 - 2.93
	CrCl <90	1.72	0.92 - 3.22	1.69	0.59 - 3.36
ABNORMAL ECG	CD4≤350cells/ml	**1.72**	**1.02 – 2.90$^{\alpha}$**	**1.84**	**1.07 – 3.10$^{\alpha}$**
	Systolic BP≥140	**2.09**	**1.18 - 3.70$^{\alpha}$**	**2.12**	**1.19 – 3.78$^{\alpha}$**
	Diastolic BP≥ 90	**1.87**	**1.07 - 3.26$^{\alpha}$**	1.55	0.71 - 2.95
	Smoker	1.57	0.30 - 8.28	1.57	0.17 - 9.11
	Diabetic	1.04	0.24 - 4.43	0.92	0.23 - 4.82
	Abnormal lipids	0.93	0.49 – 1.79	0.89	0.41 – 1.68
	HIV diagnosis ≥5yrs	0.90	0.52 - 1.55	0.85	0.45 - 1.61
	Exposure to PIs	0.85	0.36 - 2.01	1.21	0.48 - 3.04
	CrCl <90	1.23	0.72 - 2.08	1.07	0.87 - 1.92
ABNORMAL ECHO	CD4≤350 cells/ml	0.86	0.51 – 1.43	0.86	0.50 – 1.47
	Systolic BP≥140	**2.77**	**1.60 – 4.78$^{\alpha}$**	**1.47**	**1.47 - 5.75$^{\alpha}$**
	Diastolic BP≥ 90	**1.83**	**1.08 – 3.10**	0.54	0.54 - 1.88
	Smoker	0.49	0.09 – 2.50	0.12	0.12 - 3.74
	Abnormal lipids	1.07	0.57 – 2.02	0.91	0.45 – 1.99
	HIV diagnosis ≥5yrs	0.90	0.52 - 1.55	0.85	0.45 - 1.61
	Exposure to PIs	0.85	0.36 - 2.01	1.21	0.48 - 3.04
	CrCl <90	1.23	0.72 - 2.08	1.07	0.87 - 1.92

$^{\alpha}$Statistically significant

Clinical factors shown to be predictive of abnormal ECG, ECHO or ABI on multivariate logistical regression were systolic blood pressure of >140mmHg, diastolic blood pressure of >90mmHg and CD4≤350. An abnormal ABI was strongly associated with a CD4≤350, with a 2 fold increase in risk, other clinical factors did not show any such correlation. Hypertension (BP >140/90) was predictive of abnormalities on both ECG and ECHO, also showing approximately double the risk.

Diabetes, tobacco smoking and abnormal lipids which are the other known traditional CVD risk factors did not show any association with abnormal findings on ECG, ECHO and ABI.

The other non traditional CVD risk factors particularly applied to HIV infected patients such as duration of HIV infection, exposure to protease inhibitors, creatinine clearance<90, also did not show any association in this population.

DISCUSSION

This study examined the prevalence of subclinical CVD among healthy HIV infected individuals attending their routine out-patient clinic reviews. It also examined the relationship between CD4 count and the prevalence of subclinical CVD. The study population was relatively young with a mean age of 42 years and was mainly composed of female participants. Subclinical CVD was highly prevalent, a finding comparable to many studies done across Africa.[8]

The prevalence of ECG abnormalities was comparable to other major studies (53.91% vs. 51.5%); however, our population showed a fourfold higher prevalence of major abnormalities (29% vs. 7.7%).[22] Studies have found that the presence of major abnormalities on ECG has been associated with an increased risk of incident heart failure[22]. In this study, the major abnormalities found were left ventricular hypertrophy, complete left and right bundle branch blocks, atrial flutter/fibrillation, major QT prolongation and high grades of heart block (2nd and 3rd degree). The high prevalence of hypertension in this population may explain most of the ECG abnormalities especially left ventricular hypertrophy. Systolic arterial hypertension has been associated with development of pathological left ventricular hypertrophy, which may result into ventricular arrhythmias and sudden cardiac death[23]

However, this study also showed an association between CD4≤350 with significantly higher prevalence of ECG abnormalities despite the high prevalence of hypertension. Many factors may be attributed to this; evidence suggests that lower CD4 cell counts are associated with elevated levels of serum inflammatory markers and increased levels of activated CD4 T cells. This inflammatory cascade eventually leads to various forms of vascular damage and in turn causes small areas of myocardial damage.[24] As a result; many electrical abnormalities are prone to occur on ECG, independent of the usual clinical factors such as hypertension. In our study, this has been demonstrated on logistical regression where a CD4≤350 remains significant for ECG abnormalities even after adjusting for the other clinical factors.

This data therefore suggests that ECG can be used as an important tool for predicting subclinical CVD, especially in hypertensive patients with low CD4 counts, as part of their routine care.

ECHO abnormalities where found in 44.44% of our study participants; this finding was comparable to studies conducted across Africa (14 – 55%).[8] The high prevalence of left ventricular hypertrophy and left ventricular diastolic dysfunction were particularly notable. These have been associated with and increased risk of future cardiovascular events by five fold, in the general population.[20] Hypertension may be responsible for these abnormalities.

Pulmonary hypertension and pericardial effusion were not as prevalent as observed in other studies across Africa, despite the high prevalence to tuberculosis, and other HIV associated pulmonary opportunistic infections in Zambia.[25] Uncontrolled HIV infection has also been associated with direct HIV infection of the cardiac myosites, leading to the development of HIV associated dilated cardiomyopathy (DCM), which is said to progress rapidly to death within 100 days of diagnosis.[26] However in this population, no patient had DCM, except for a few found with left ventricular systolic dysfunction. A low CD4 count did not show an association with increased prevalence echo abnormalities in this population.

ECHO is an important tool for assessing both cardiac structure and function. However, due to its non availability in most hospitals in the country and requirement of particular expertise, using it as a screening tool might be a challenge, notwithstanding the cost implications. As such, only those HIV patients found to have several CVD risk factors, low CD4 counts and major

changes on ECG may benefit from a baseline ECHO study.

Peripheral artery disease has been shown to be associated with future incident cardiovascular events particularly ischemic strokes and myocardial infarction.[27,28] This condition can be screened for using Ankle Brachial Index (ABI). Our study population showed a similar prevalence of abnormal ABI as other major studies (20.1% vs. 19%).[29] In addition, a CD4≤350, was associated with a 2 fold increase in risk. This may be explained as follows; normally, activated CD4 T cells are found frequently in atherosclerotic plaques of patients in the general population. However, the chronic inflammation that accompanies uncontrolled or more advanced HIV disease consists of many of the same inflammatory cells and pro-inflammatory cytokines that destabilize atherosclerotic plaques. In addition, the chemokine receptor CCR5 on the HIV is immunogenic and resides in the intima and media of arteries. It is said to trigger an inflammatory cascade that results in plaque rupture and coronary artery thrombosis by directing monocytes and recruiting T cells to these arteries.[24, 30, 31] Therefore uncontrolled HIV infection is a risk factor for accelerated atherosclerosis. Studies have shown that an ABI<0.9 is associated with stenosis of ≥50% of the affected artery, it is also a marker of systemic atherosclerosis, which predisposes to future coronary artery disease events and ischemic strokes.[29]

ABI is a cheap tool that has been validated by many population studies; [29] it can be easily administered by caregivers at a primary health care level with minimal expertise. As such, all HIV positive patients especially those with CD4≤350 would benefit from a routine measurement of the ABI.

According to the Framingham heart study of 1961, traditional CVD risk factors are hypertension, diabetes, high cholesterol and smoking; these have been associated with increased risk of future CVD events.[24] In our study population, the commonest traditional CVD risk factor was hypertension, and this value increased two fold during physical examination, meaning most of these participants had undiagnosed hypertension. Furthermore, hypertension was the only traditional CVD risk factor which showed a significant association with abnormalities on all the three screening tools used in this study, the other risk factors, in particular, diabetes and tobacco smoking did not. This may however be explained by the low prevalence of these conditions in our study participants. This finding is important in that it draws attention to hypertension as being the most important traditional CVD risk factor in this population, and that more effort needs to be made to screen for it and treat it at every opportunity.

Other non- traditional CVD risk factors among HIV infected patients known to increase risk of CVD as demonstrated by various studies include duration of HIV infection[32], exposure to protease inhibitors[41], kidney disease[53] and low CD4 count[24,34]. In our population, a low CD4 count (≤350cells/ml) was associated with a 2 fold risk of having an abnormal ABI and ECG. The other clinical factors did not show such an association.

STUDY LIMITATIONS

This was a single centre study, therefore findings cannot be generalised to the entire Zambian HIV population. We were also unable to do viral load test to compare with CD4 counts and how this would relate to subclinical CVD. Most of our blood tests were limited to routine tests done on all HIV patients attending clinic, we were unable to do more specific tests which are biomarkers of heart disease such as d-dimer, C-reactive protein, or test for the presence of opportunistic infections associated with heart disease. All these were due to budgetary constraints.

We did not have a suitable HIV seronegative control group, but however we found higher than expected prevalence rates for subclinical CVD in HIV infected people, compared with general population data.[12]

CONCLUSION

Subclinical CVD is quite common among clinically healthy HIV infected patients attending their regular out-patient clinic visits at UTH. All 3 tools of measurement used in this study have been able to detect significant numbers of subclinical disease, with ECG showing the highest prevalence. Of the traditional CVD risk factors, hypertension is the most common, while diabetes and smoking have low prevalence. On the non traditional CVD risk factors, CD4≤350 is the most important risk factor in this population.

RECOMMENDATIONS

In view of the high prevalence of subclinical CVD in this relatively healthy HIV infected population, we make the following recommendations:

- Screening for and treatment of hypertension must be conducted at each clinic visit.
- To perform ABI measurements on all patients coming for their first enrollement and on all those with CD4≤ 350 and BP >140/90mmHg even if they are on treatment. ABI measurement is very simple tool and can be done by primary health care workers at no cost to the patient.
- All patients with CD4≤ 350 and BP>140/90 should undergo a baseline ECG if available
- All patients with abnormal ECG especially major abnormalities such as left ventricular hypertrophy, major QT prolongation, Q waves, major arrhythmias (complete bundle branch blocks, 2nd and 3rd degree heart blocks, atrial flutter/fibrillation) must undergo a routine baseline ECHO.
- To evaluate the cost effectiveness of using ECG, ECHO and ABI as screening tools for CVD across Zambia.
- A long term study needs to be conducted to determine the outcomes of patients with these various abnormalities.

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