# Patterns of cardiovascular disease in a group of HIV-infected adults in Yaoundé, Cameroon

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**Background:** Cardiovascular disease is an increasingly important issue in human immunodeficiency viral (HIV)-infected individuals. There is dearth of information on the patterns of cardiovascular disease especially in sub-Saharan Africa (SSA) patients. This study reports on the clinical, biological, electrocardiographic and echocardiographic characteristics of a group of HIV-infected patients presenting with symptoms of heart disease in Yaoundé, Cameroon.

**Methods:** This was a cross-sectional study conducted at the Yaoundé Central Hospital and Jamot Hospital. Consenting HIV-infected adults aged ≥18 years with symptoms suggestive of heart disease were consecutively recruited between February and July 2014. All participants underwent a complete clinical examination; biological analyses including CD4 cell counts, fasting blood glucose, and serum lipids, resting electrocardiography and cardiac ultrasound, and a venous ultrasound where necessary.

**Results:** Forty four subjects (21 men) were included. Their mean age was 48 (SD 13) years. Thirty patients (68.2%) were in WHO clinical stages 3 and 4 of HIV infection, 27 (61.4%) had a CD4 cell count <200/mm$^3$, and 31 (70.5%) were on antiretroviral therapy (ART). Hypertension (43.2%, n=19) was the most frequent cardiovascular risk factor; and dyslipidemia which was found in 17 subjects (38.6%) was significantly associated with ART (48.4% *vs.* 15.4%, P=0.04). Only men where smokers (23% *vs.* 0%, P=0.019). Exertional dyspnea (86.4%, n=38) and cough (59.1%, n=26) were the most frequent symptoms, and the clinical presentation was dominated by heart failure (75%, n=33). The most frequent echocardiographic abnormalities were pericardial effusion (45.5%, n=20) and dilated cardiomyopathy (22.7%, n=10). Dilated cardiomyopathy was significantly associated with CD4 cell counts <200/mm$^3$ (100%, P=0.003). Primary pulmonary hypertension (PH) rate was 11.4% (n=5) and all cases occurred at CD4 cell counts ≥200/mm$^3$ (P=0.005). The most frequent electrocardiographic abnormalities were abnormal repolarization (59%, n=26) and sinus tachycardia (56.8%, n=25).

**Conclusions:** Cardiovascular risk factors such as hypertension and dyslipidemia are common in HIV-infected adults with heart disease in our milieu. Advanced HIV infection in adults is associated with a high rate of symptomatic heart disease, mostly effusive pericarditis and dilated cardiomyopathy. Primary PH occurred in less advanced HIV disease.

**Keywords:** Cardiovascular disease; HIV/AIDS; echocardiography; electrocardiography; Cameroon

## Introduction

Human immunodeficiency viral (HIV) infection is a worldwide public health problem with the greatest impact on low income countries (1-3). Increasing access to antiretroviral therapy (ART) has decreased HIV disease associated deaths and increased survival thus making HIV infection a chronic disease (4,5). HIV infection and the metabolic effects associated with ART add to the rising burden of cardiovascular disease in low income countries (6,7). Cardiovascular disease is seen in 30-80% of HIV infected adults, depending on the working definition, screening method, and severity of HIV disease (8). In patients with heart disease, up to 9.7% of patients are infected with HIV (9). All heart structures are involved, and the severity of which correlates with that of immune deficiency (10,11). The pathogenesis of heart disease during HIV infection is multifactorial with the interplay of host cardiovascular risk factors, ART, and HIV infection (12). In the context of increasing availability of ART for patients even at early stage of HIV infection, as deaths due to HIV-associated opportunistic infections are decreasing, increased rates in mortality due to HIV-associated cardiovascular disease are expected among HIV-infected adults. Yet, epidemiological data on cardiovascular disease in HIV-infected individuals are still scare, especially in low-income countries such as Cameroon.

Like other developing countries, Cameroon is experiencing a surge in the prevalence of hypertension, diabetes and other cardiovascular risk factors, and consequential cardiovascular disease (13-16). Ill-prepared health care system, out-of-pocket payments and unaffordable care, and non-optimal management of cardiovascular risk factors by health care providers are major impediments to cope with the rising burden of cardiovascular disease in the country (17-20). Besides, Cameroon is still confronted with a high burden of communicable diseases, especially HIV infection with a national prevalence of 4.3% (2). This work aimed at reporting the baseline clinical, electrocardiographic, and echocardiographic characteristics of cardiovascular disease associated with adult HIV infection in a resource limited setting in Yaoundé, Cameroon.

## Methods

### Ethical statement

This study was approved by the Institutional Review Board of the Université des Montagnes, ethical clearance N° 2014/60/UdM/PR/CAB/CIE. The study was conducted in accordance with the Helsinki declaration.

### Study design, setting, and participants

This was a cross-sectional study carried out between February and July 2014 in the Yaoundé Central Hospital and Jamot Hospital which are two teaching hospitals in Yaoundé, the capital city of Cameroon, and a low income setting in sub-Saharan Africa (SSA). Eligible subjects were consenting adults with confirmed HIV infection, aged ≥18 years, presenting with symptoms suggestive of heart disease according to the Framingham clinical diagnostic criteria (21), treated or not treated with antiretroviral medications. Pregnant women and those with known heart disease were excluded.

### Procedures

All eligible participants underwent a complete clinical evaluation searching for other elements of cardiovascular disease. We measured resting blood pressures using standardized procedures with the participant in a seated position, and after at least 10 min rest with a mercury sphygmomanometer. The mean of two measures performed at least 3 min apart was used for all analyses. We measured weight in light clothes with a Seca® scale balance to the nearest 0.1 kg, height with a calibrated stadiometer to the nearest 0.5 cm. After 8-12 h overnight fast, blood glucose was measured on total fresh capillary blood samples using the Accu-Chek® Compact Plus glucometer (F. Hoffmann-La Roche AG, Basel, Switzerland), and venous blood samples were drawn from an ante brachial vein for biochemical analyses. Serum lipids including total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol and triglycerides were measured using a Vitros 350 chemistry analyzer (Ortho-Clinical Diagnostics), and CD4 cell counting using a FACS counter. A resting 12-lead electrocardiogram was then performed following standard procedures (speed regulation of 25 mm/s and voltage regulation of 10 mV/10 mm) using a SMART electrocardiograph. A transthoracic cardiac ultrasound was performed with the patient in the left lateral decubitus position by the same cardiologist (APM) using a Philips Sonos 7,500 color Doppler ultrasound machine, initially blinded to the ECG. This was in accordance with the American Society of Echocardiography recommendations (22). A VOLUSON

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730 Pro V ultrasound machine with a 50/60 Hz probe was used to study limb vessels in those with suspected deep venous thrombo-embolic (VTE) disease.

### Measurements and definitions

Smoking was defined as current tobacco use or use during the last 3 months. Physical activity was defined as at least 150 min of moderate-intensity aerobic physical activity throughout the week or at least 75 min of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity (23). Patients who did not fulfill this definition were considered physically inactive. We defined hypertension according to World Health Organization recommendation (24) as a resting systolic blood pressure (SBP) ≥140 mmHg and or diastolic blood pressure (DBP) ≥90 mmHg or a patient on antihypertensive treatment. We defined diabetes mellitus as a fasting blood glucose >1.26 g/L at least two time or a patient on antidiabetic treatment (25). We defined overweight as a body mass index (BMI) between 25 and 29.9 $kg/m^2$ and obesity as a BMI ≥30 $kg/m^2$. We defined dyslipidemia as total cholesterol ≥200 mg/L, or triglycerides ≥150 mg/L, or LDLC ≥160 mg/L, or HDLC <40 mg/L in men or <50 mg/L in women. Left ventricular (LV) dilation was defined as indexed LV diameter in diastole >34 $mm/m^2$, and left atrial (LA) enlargement as LA diameter >2.6 $mm/m^2$. Right Ventricular (RV) dilation was defined as RV diastolic area >32 $cm^2$. Pulmonary hypertension (PH) was defined as PAH ≥35 mmHg. Primary PH was considered when there is no evidence of any left heart disease or other possible causes of PH. LV hypertrophy (LVH) was defined as an indexed LV mass (LVMI) >131 $g/m^2$ in men and LVMI >108 $g/m^2$ in women. LV systolic dysfunction was defined as an ejection fraction <45% and RV systolic dysfunction was defined as a Tei myocardial performance index of >0.4. We used Appleton's criteria to diagnose and classify LV diastolic dysfunction (26). Valves for vegetations, stenosis and insufficiency, global and segmental motions, as well as the presence of intra-cavity thrombus were also studied. The diagnosis of myocarditis was made on clinical arguments of signs of inflammation, electrocardiographic and echocardiographic arguments of low LV ejection fraction, global hypokinesia without dilation of the cavities. No magnetic resonance imaging (MRI) or endomyocardial biopsy was performed

in the diagnosis of myocarditis. The diagnosis of dilated cardiomyopathy was made in the presence of low ejection fraction and dilated left ventricle on echocardiography and the absence of any plausible explanation. Ischemic heart disease was diagnosed based on clinical arguments of exertional chest pain, ECG ST segment and T wave changes, and segmental wall motion anomaly on echocardiography. No coronary angiogram was performed as it is not available in our setting. Pericarditis with effusion was made on echocardiography when an echo free space was present between the visceral and parietal pericardium during the entire cardiac cycle. It was considered mild when it measured less than 1 cm, and large when it measured more than 2 cm. No pericardial fluid puncture was made for diagnostic purpose. In our context, this procedure is done only for cases of pericardial tamponade. Tachycardia was defined as a heart rate >100 beats per minute. ECG LVH was defined using Cornell index ($RaVL + SV_3$) >28 mm in men and 20 mm in women. ECG RVH was defined as R/S ratio >1 in $V_1$ or <1 in $V_5$ or $V_6$. Other ECG anomalies studied were repolarization anomalies, presence irregular baseline with irregular rhythm suggestive of atrial fibrillation, or saw tooth baseline suggestive of atrial flutter, premature atrial or ventricular contractions, P wave duration and morphology for atrial enlargement, R wave progression, ST segment abnormalities and presence of $S_1Q_3$ wave pattern.

### Data analysis

Data were analyzed using Epi Info version 3.5.4 software. Quantitative variables were compared using the Mann-Whitney test, and Pearson's Chi-squared test of independence was used to study the relationship between qualitative variables. We presented qualitative data as frequencies and proportions, and quantitative data as means with standard deviations (SD). A P value <0.05 was considered statistically significant.

### Results

We enrolled 53 HIV-infected patients presenting with symptoms of heart disease, of which 44 were included in data analysis. Nine were lost to follow up after the first visit thus, excluded due to incomplete data. The clinical characteristics are summarized in *Table 1*. Twenty one (48%) of the patients were men, with an overall mean age of 48.5 (SD 13.1) years (range, 24-72 years). Twenty four

**Table 1** Clinical characteristics and cardiovascular risk factors in the study population

| Variables | Frequency (%) or mean ± standard deviation |
|---|---|
| Mean age | 48±13.1 |
| Age range (years) | |
| ≤25 | 2 (4.5) |
| 26-45 | 17 (38.7) |
| 46-65 | 22 (50.0) |
| >65 | 3 (6.8) |
| Average CD4 cell counts/mm$^3$ | 205±187.9 |
| Proportion of CD4 cell counts | |
| ≤200 | 27 (61.4) |
| 200-350 | 10 (22.7) |
| >350 | 7 (15.9) |
| Duration of known HIV status (months) | |
| <1 | 7 (15.9) |
| 1-12 | 13 (29.5) |
| >12 | 24 (54.5) |
| WHO clinical stage | |
| 1 | 6 (13.6) |
| 2 | 8 (18.2) |
| 3 | 11 (25.0) |
| 4 | 19 (43.2) |
| Proportion on ART | 31 (70.5) |
| Average duration on ART (months) | 33.7±39.3 |
| Cardiovascular risk factors | |
| Physical inactivity | 27 (61.4) |
| Hypertension* | 19 (43.2)* |
| Dyslipidemia¥ | 17 (38.6)¥ |
| Obesity | 8 (18.2) |
| Tobacco use (active)# | 5 (11.4)# |
| Diabetes | 2 (4.5) |
| Positive family history | 1 (2.3) |
| Symptoms of cardiovascular disease | |
| Exertional dyspnea | 38 (86.4) |
| Cough | 26 (59.1) |
| Palpitations | 24 (54.5) |
| Chest pains | 21 (47.7) |
| Orthopnea | 14 (31.8) |
| Exertional painful liver | 11 (25.0) |
| Leg pains | 8 (18.2) |
| Syncope | 8 (18.2) |

**Table 1** (continued)

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| Variables | Frequency (%) or mean ± standard deviation |
|---|---|
| Hemoptysis | 2 (4.5) |
| Paroxysmal nocturnal dyspnea | 2 (4.5) |
| Signs of cardiovascular disease | |
| Left deviation of the apical impulse | 12 (27.9) |
| Muffled heart sounds | 12 (27.9) |
| Heart murmurs | 10 (23.3) |
| Arrhythmia | 8 (18.6) |
| Signs of deep venous thrombosis (Wells criteria) | 8 (18.6) |
| Loud second heart sound at pulmonary area | 4 (9.3) |
| Pericardial rub | 0 (0) |
| Signs of heart failure (at least one sign ) | 32 (74.4) |

*, higher in females (28.6% *vs*. 56.5%, P=0.058); ¥, significantly higher in patients on antiretroviral therapy (48.5% *vs*. 15.4%, P=0.040); #, significantly higher in men (23% *vs*. 0%, P=0.019). HIV, human immunodeficiency viral; ART, antiretroviral therapy.

patients (54.5%) were diagnosed with HIV for more than 1 year, and 27 (61.4%) had CD4 cell counts <200/mm$^3$. Thirty one (70.5%) patients were on ART, of whom 28 (90.3%) were on first line treatment comprising various combinations of Zidovudine, Lamivudine, Stavudine, Tenofovir, Didanosine, with Nevirapine and Effavirenz. Three patients on second line treatment including first line ART drugs with Lopinavir and Ritonavir. The most frequent cardiovascular risk factors were physical inactivity (61.4%, n=27), hypertension (43.2%, n=19) and dyslipidemia (38.6%, n=17). Hypercholesterolemia, low HDL-cholesterol, hypertriglyceridemia, and high LDL-cholesterol were seen in 8 (18.2%), 11 (25%), 9 (20.5%), and 5 (11.4%) patients respectively. Dyslipidemia was significantly more frequent in ART-treated patients (48.4% *vs*. 15.4%, P=0.04). The most frequent symptom was exertional dyspnea seen in 38 (86.4%) of patients, with 36.8% in stage II, 26.3% in stage III, and 36.9% in stage IV (New York Heart Association classification). The electrocardiographic and echocardiographic findings are summarized in *Table 2*. Forty one patients (93.2%) had an abnormal ECG, and the most frequent anomalies were abnormal repolarization seen in 26 (59%) and sinus tachycardia seen in 25 (56.8%) patients.

**Table 2** Electrocardiographic and echocardiographic findings

| Findings | Frequency (%) |
|---|---|
| Electrocardiographic findings | |
| Abnormal repolarization | 26 (50.9) |
| Sinus tachycardia | 25 (56.8) |
| Left ventricular hypertrophy | 13 (29.5) |
| Conduction anomalies* | 11 (25.0) |
| Arrhythmias** | 9 (20.4) |
| Low voltages | 8 (18.1) |
| Slow progression of R wave | 3 (6.8) |
| Right ventricular hypertrophy | 3 (6.8) |
| Right atrial enlargement | 3 (6.8) |
| $S_1Q_3$ aspect | 1 (2.3) |
| Left atrial enlargement | 1 (2.3) |
| Echocardiographic findings | |
| Pericardial effusion[$] | 20 (46.5) |
| Left ventricular systolic dysfunction | 16 (37.2) |
| Pulmonary artery systolic pressure ≥35 mmHg*** | 13 (30.2) |
| Dilated right heart chambers | 11 (25.6) |
| Dilated left heart chambers | 10 (22.7) |
| Left ventricular diastolic dysfunction | 9 (20.5) |
| Left ventricular hypertrophy | 5 (11.4) |
| Valvular insufficiency[#] | 4 (9.1) |
| Global hypokinesia | 4 (9.1) |
| Segmental hypokinesia | 2 (4.5) |
| Intracardiac thrombus | 2 (4.5) |
| Valvular vegetations (mitral valve only) | 2 (4.5) |

[$], 4 patients had large (>2 cm) effusions; *, 4 left anterior hemi-fascicular block, 5 complete right bundle branch block, 2 complete left bundle branch block, 2 first degree A-V block; **, 1 atrial fibrillation, 2 atrial flutter, 2 supra-ventricular extrasystoles, 6 ventricular extrasystoles; ***, 5 had no identified cause, thus considered as primary pulmonary hypertension; [#], 2 patients with mitral valve vegetations, and 2 patients with functional valve insufficiency.

All patients had an abnormal echocardiogram. The most frequent echocardiographic abnormalities were pericardial effusion (46.5%, n=20), and dilated cardiomyopathy (22.7%, n=10). Lower limb venous ultrasound was performed in 11 patients; deep venous thrombosis was seen in 8 (18.2%), which was mainly proximal. There was no right or left predominance in thrombus location. The association

of cardiovascular disease findings with CD4 cell counts is summarized in *Table 3*. Dilated cardiomyopathy was significantly associated with low CD4 cell counts (<200/mm³) (100%, P=0.003). Primary PH only occurred at levels of CD4 cell counts >200/mm³ (100%, P=0.005).

## Discussion

We found high rates of traditional cardiovascular risk factors and symptomatic cardiovascular disease associated with severe immune deficiency in this young adult population infected with HIV, most of who were on ART for close to three years. The spectrum of cardiac disease in HIV infection varies between studies within and between countries (27). This could be explained by the complex interactions between the traditional cardiovascular risk factors, HIV infection, level of immunity, and antiretroviral treatment. Differences in the methodology used as well as ethnicity could also explain the observed differences. Participants were all young, between the ages of 35 and 45 years, and the most frequently seen conditions were cardiomyopathies, pericardial disease, and PH in varying proportions (6-9,11,27). Other cardiovascular conditions such as coronary heart disease (myocardial infarction in our study) were less frequent and less reported. Valvular heart diseases were not clearly characterized. Common conditions in HIV infection like VTE diseases were less frequently reported.

Few studies in SSA have addressed the problem of classical cardiovascular risk factors in HIV infected adults. Edward *et al*. reported a moderate to high 10-year cardiovascular risk of 12.8%, predominated by sedentary, and dyslipidemia, with rates similar to our findings (28). Dyslipidemia was frequently seen in those on antiretroviral treatment. Our subjects presented with higher rates of hypertension, obesity, and tobacco use. Smoking rate was lower than that reported by Chillo *et al*. (29), and it was entirely a male phenomenon as shown by both studies. There could be an under reporting in the rate of tobacco, as its use by women is not a widely accepted practice in SSA. Physical inactivity was very frequent, probably because more than half of the patients had advanced HIV infection and therefore physically and mentally debilitated by ill health. The small sample size of this study could also lead to over estimation of the cardiovascular risk factors.

Cardiomyopathy rates varied widely, ranging from 5% to 57% (12). It has been shown to be associated with worsening immunity, almost exclusively seen when CD4 cell counts are <200/mm³ (11) consistent with our finding. Ayaskanta *et al*. (11)

**Table 3** Association of cardiovascular diseases and CD4 cell counts

| Cardiovascular disease | CD4 cell count/mm$^3$ of blood | | | | Total, n (%) | P* |
|---|---|---|---|---|---|---|
| | >500 | 200-499 | 50-199 | <50 | | |
| Effusive pericarditis | 1 | 4 | 6 | 9 | 20 (46.5) | 0.082 |
| Myocarditis | 0 | 1 | 1 | 2 | 4 (9.1) | 0.496 |
| Dilated cardiomyopathy | 0 | 0 | 2 | 8 | 10 (22.7) | 0.003 |
| Endocarditis | 0 | 0 | 0 | 2 | 2 (4.5) | 0.371 |
| Primary pulmonary hypertension | 2 | 3 | 0 | 0 | 5 (11.4) | 0.005 |
| Myocardial infarction | 0 | 2 | 0 | 0 | 2 (4.5) | 0.144 |
| Deep venous thrombosis | 0 | 2 | 5 | 1 | 8 (18.2) | 0.325 |
| Pulmonary embolism | 0 | 3 | 2 | 1 | 6 (13.6) | 0.462 |
| Hypertensive heart disease | 1 | 3 | 0 | 1 | 5 (11.4) | 0.065 |

*, P values computed for CD4 cut off value of 200 cells/mm$^3$.

showed a moderate upward and significant correlation between LV ejection fraction/shortening and CD4 cell counts. This suggests that cardiomyopathy is a marker of severe immune deficiency in HIV disease. The pathogenesis is complex, with interplay of host and viral factors (9,27). It is not clearly known whether improved CD4 cell counts on ART improves on the heart structure and function.

Effusive pericarditis does not seem to correlate with the degree of immune deficiency. It is not significantly associated with low CD4 cell counts <200/mm$^3$ (7,8,29) consistent with our finding. Effusive pericarditis is mainly due to tuberculosis (27).

Primary PH is a frequently reported disease and occurs early in HIV infection (8,30) consistent with our finding. It is associated with poor outcome as specific treatment is economically unavailable to the SSA patient.

VTE disease is under diagnosed and under reported, and it could be responsible for a non-negligible cause of morbidity and mortality in this group of patients. Anzouan-Kacou *et al*. (8) reported a prevalence rate of 15.5%, slightly lower than our finding, with a small proportion of pulmonary embolism, and Niakara *et al*. (6) reported a small rate of 3.8%. It was not related to low CD4 cell counts in this study.

The proportion of coronary artery disease (myocardial infarction) was higher in our study compared to that reported by other authors in SSA. It occurred at higher levels of CD4 cell counts. This could be indirectly related to HIV infection via the classical cardiovascular risk factors. Also, the relative small sample size of our study could lead to a relatively higher rate.

This study has some limitations. The cross-sectional and descriptive design does not permit us to establish a cause and effect relation between HIV infection and the observed patterns of heart disease. The small sample size does not give enough power to establish a significant association of HIV infection and some observed disease conditions. The viral load was not measured, which could have contributed to a better understanding of the pathophysiological mechanisms of HIV infection and cardiovascular disorders. Invasive tests to ascertain the diagnosis of myocarditis, pulmonary embolism, and PH were not performed due to insufficient finance to pay for such tests. More so, some of these procedures are not available in this low-income setting. Despite these shortcomings, this study adds to the existing rare information on HIV and cardiovascular diseases in SSA. Patients were prospectively recruited, and all underwent rigorous evaluations and testing using the same instruments and by the same operators, thus ensuring homogeneity and reliability of the collected data.

## Conclusions

Cardiovascular risk factors such as hypertension and dyslipidemia are common in HIV-infected adults with heart disease in our milieu. Advanced HIV infection in adults is associated with a high rate of symptomatic heart disease, mostly effusive pericarditis and dilated cardiomyopathy. Primary PH occurred in less advanced HIV disease.

## Acknowledgements

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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