Brief Report

Cardiovascular risk and D-dimer levels in HIV-infected ART-naïve Africans

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Abstract: Anti-retroviral therapy (ART) has decreased morbidity and mortality in HIV-infected individuals. With the adoption of the 90-90-90 strategy prevention and control of non-communicable disease, particularly knowledge of the burden and profile of cardiovascular disease, will become increasingly important. Our study assessed cardiovascular risk among recently diagnosed HIV-infected ART-naïve patients in a first referral urban hospital in a low-income country in sub-Saharan Africa. HIV-positive ART-naïve patients were submitted to cardiovascular risk assessment, clinical history, physical examination and laboratory workout, including 12-lead electrocardiography, portable transthoracic echocardiography, glycemia, lipidemia, hemogram and D-dimers. Three years after the diagnosis their vital status and occurrence of major cardiovascular events was assessed. We recruited 70 patients, all of black ethnicity (41 females; mean age 37±10.7). CD4 levels were very low (mean 21.3 cells/mL; SD 10.4). Twenty-one (26.6%) were overweight, 13 (16.7%) were obese, 19 (20.5%) had hyperglycemia and 20 patients (25.6%) had hypercholesterolemia. The median blood pressure was 119.5/79 mmHg (IQR 107-141/67-83); 20 patients (25.6%) had hypertension. Four (5.7%) patients had signs of heart failure, and left ventricular ejection fraction was reduced in 17 (25%). High levels of circulating D-dimers were found in 44 (62.8%) patients; the mean levels were 725.9 (SD 555.1). We found high occurrence of cardiovascular risk factors, left ventricular dysfunction and evidence of a pro-coagulant state in these HIV-infected ART-naïve patients. Active cardiovascular risk screening and stratification, as well as management protocols tailored to low-income settings are needed to sustain the gains obtained with increased availability of ART in Africa.

Keywords: HIV; cardiovascular risk; thrombotic markers

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Introduction

The World Health Organization (WHO) supports the initiation of antiretroviral treatment (ART) for all HIV-infected individuals, independent of their immunologic or clinical status (1). Throughout sub-Saharan Africa (sSA) countries have adopted the "Test-and-Treat" strategy (2), which is expected to contribute to achieving UNAIDS 90-90-90 treatment targets (3). Studies from sSA have highlighted the role of ART in reducing HIV/AIDS-associated morbidity and mortality (4-10), but late presentation to health facilities remains a challenge, maintaining a high risk of death despite availability of effective treatment (4,8,9). With the expansion of ART in Africa cardiovascular disease (CVD) and thrombotic events replaced tuberculous pericarditis and dilated cardiomyopathy as major causes of mortality in the HIV-infected (11-13).

HIV prevalence is over 10% in adult population in Mozambique (14), a country lacking specialized human resources (15), infrastructure for chronic care and NCD surveillance system. The WHO Stepwise Approach to Surveillance (STEPS) surveys of cardiovascular risk factors,

revealed high prevalence of hypertension, obesity and alcohol consumption (16-18). In adults 25–64 years old the prevalence of hypertension is 38.9% (19), 3.8% have diabetes and concerning levels of overweight (27.1%) and obesity (10.8%) occur in females (20). We therefore designed a study to assess cardiovascular risk among recently diagnosed HIV-infected ART-naïve patients.

Methods

Between 21/05/2015 and 21/12/2015 HIV-positive ART-naïve adult patients diagnosed in WHO classification clinical stage I–II (21) were recruited at a first level referral urban hospital in Maputo, Mozambique. HIV infection was documentated by any licensed ELISA test kit and confirmed by a second method (Western blot). Cardiovascular risk assessment, clinical history and physical examination were performed, including 12-lead electrocardiography and portable transthoracic echocardiography. Left ventricular systolic dysfunction was as defined by left ventricular ejection fraction ≤45% and/or fractional shortening <25%. Venous blood was obtained to measure CD4 count, hemoglobin, glycemia and lipids. A cut-off point of hemoglobin less than 13 (males) and less than 12 (females) was used to define anemia; values lower than 8.0 g/dL defined severe anemia for both sexes. Approximately 1mL of blood obtained from digital puncture was used to determine D-dimers levels using rapid tests (Cobas h 232 PoC handset system - Roche). D-Dimmer was age-adjusted for patients over 50 years [using the formula age (years) × 10 µg/L] (22); values >500 ng/mL were considered abnormal.

All patients initiated ART after the diagnosis as per local management protocols. From May 2018 to August 2018 we assessed the vital status of all participants and the occurrence of major cardiovascular events.

Statistical analysis

Descriptive statistics were computed for demographic, laboratory, echocardiography and HIV-related parameters. Quantitative variables are described with mean (SD) or the median (IQR). To analyze patient's characteristics by gender, Kruskall Wallis non-parametric test was used to compare medians and *t*-test to compare means; for qualitative variables Qui-square or Fisher tests were performed. Analyses were done with STATA software and using a 5% significance level.

Ethical considerations

The national bioethics committee approved the study. Informed consent was obtained from all participants.

Results

We recruited 70 patients (41 were females; mean age 37 years, SD 10.7; all of black ethnicity).

Risk factors profile

Three male were smokers. The mean abdominal circumference was 84 cm (SD 10); 21 patients (26.6%) were overweight and 13 (16.7%) obese. The median blood pressure was 119.5/79 mmHg (IQR 107-141/67-83); 20 patients (25.6%) had hypertension. Hypercholesterolemia was present in 20 patients (25.6%)—9 (11.5%) with levels over 7.8 mmol/L—and hypertriglyceridemia in 16 (20.5%). Nineteen patients (20.5%) had hyperglycemia, of which 9 (11.5%) had diabetes. Mean CD4 levels were very low (mean 21.3 cells/mL; SD 10.4). Moderate anemia was found in 28 patients (35.9%) and severe anemia in only one. The median (IQR) hemoglobin level was 11.45 g/dL (9.8–12.8) [12.4 (10.4–13.6) in men *vs.* 11.1 (9.8–12.2) in women]. There was no difference in levels of blood pressure, glycaemia or cholesterol between males and females; women had lower triglyceride levels (1.3 *vs.* 1.0 mmol/L, P=0.04) (*Table 1*).

Cardiac function and biomarkers

Severe impaired left ventricular systolic function was found in 9 patients (shortening fraction below 25%) of which 4 had signs of congestive heart failure. D-dimer levels did not differ between patients with severely impaired left ventricular systolic function [9] and those with normal ventricular function [61], with median 486.67 *vs.* 548.08 ng/mL, respectively (P=0.93). Three patients had high troponin T levels, but none had clinical or electrocardiographic signs of ischemic heart disease.

Pro-thrombotic markers

High D-dimers levels were found in 44 (62.8%) patients. The mean D-dimers level was 725.9 ng/mL (SD 555.1). No difference was found according to gender—606.6 (SD 411.7) males *vs.* 810.4 (SD 628.7) females; P=0.934.

Table 1 Risk profile, clinical features and laboratory results of the 70 patients HIV-infected ART-naïve patients with distribution by gender

Variables	All	Males	Females	P value
Patients characteristics				
Sex, n (%)	70	29 (41.4)	41 (58.6)	–
Age (years), mean (SD)	37.14 (10.7)	36.5 (10.5)	37.6 (10.9)	0.6582
Abd circumference (cm), mean (SD)	84.07 (10)	84.3 (9.2)	83.9 (10.6)	0.4339
Risk factors profile				
Body mass index, n (%)				0.0153
Underweight	8 (10.1)	4 (13.8)	4 (9.8)	
Normal	37 (46.8)	19 (65.2)	18 (43.9)	
Overweight	21 (26.6)	6 (20.7)	15 (36.6)	
Obese	13 (16.5)	0 (0.0)	4 (9.8)	
High blood pressure, (>140/>90 mmHg), n	20	9	11	–
Systolic BP mmHg, median (IQR)	119.5 (107–141)	125 (110–141)	119 (104–139)	0.4419
Diastolic BP, median (IQR)	79 (67–83)	77 (70–84)	79 (66–83)	0.7745
Fasting Glucose (mmol/L), median (IQR)	4.51 (4.2–5.29)	4.46 (4.2–5.4)	4.53 (4.23–5.03)	0.7792
CD4 (cells/mL), mean (SD)	21.3 (10.4)	21.5 (9.5)	21.2 (11.0)	0.4588
Signs of heart failure, n (%)				0.720
No	66 (94.3)	27 (93.1)	39 (95.1)	
Yes	4 (5.7)	2 (6.9)	2 (4.9)	
Heart rate (bpm), median (IQR)	80 (70–89)	81 (75–91)	80 (69–88)	0.7231
Cardiothoracic Index >55%	8 (11.4%)	4 (13.8)	4 (9.8)	1.00
Laboratory results				
Hemoglobin (g/dL), median (IQR)	11.45 (9.8–12.8)	12.4(10.4–13.6)	11.1 (9.8–12.2)	0.04
MCV (fL/red cell), mean (SD)	77.4 (13.6)	78.7 (11.9)	76.4 (14.8)	0.2506
MCHC (g/dL), mean (SD)	33.5 (8.2)	32.9 (1.5)	33.9 (10.7)	0.691
Cholesterol (mmol/L), mean (SD)	3.8 (1.1)	3.6 (1.2)	3.9 (1.1)	0.882
Triglyceride (mmol/L), mean (SD)	1.1 (0.7)	1.3 (1.0)	1.0 (0.3)	0.04
Troponin (qualitative) >0.05, n (%)	3 (4.3)	2 (7.1)	1 (2.4)	1.00
D-Dimers (ng/mL), mean (SD)	725.9 (555.1)	606.6 (411.7)	810.4 (628.7)	0.934
Echocardiographic features				
LVEF, n (%)				0.0095
Normal	53 (75.0)	24 (92.3)	29 (87.9)	
Mild dilatation	1 (1.4)	0 (0.0)	1 (3.0)	
Moderate dilatation	4 (5.7)	2 (7.7)	2 (6.0)	
Severe dilatation	1 (1.4)	0 (0.0)	1 (3.0)	

Abd, abdominal; IQR, interquartile range.

Table 2 Baseline demographic and clinical characteristics of HIV patients with adverse outcomes (hospitalization or deaths) over a period of 2 years after diagnosis

Patient	Age (y)	Sex	Smoker	BMI	EF (%)	CD4 cell/mm^3	D-dimer	Adverse events	Death
02	32	F	No	23.0	20.0	39	1380	DVT	No
04	40	M	No	24.5	19.2	39	209	HF	Yes
20	50	M	No	25.5	57.0	7	528	HF	No
24	70	M	No	25.5	46.4	29	1165	HF	Yes
33	32	M	No	19.2	57.4	20	468	Stroke	No
43	36	M	Yes	23.6	80.0	24	1238	Unknown	Yes
57	32	M	Yes	23.5	63.2	26	1697	Tuberculosis	Yes
70	42	F	No	33.0	64.2	10	792	Unknown	Yes

M, male; F, female; BMI, body mass index; EF, ejection fraction; HF, heart failure; DVT, deep venous thrombosis.

Follow-up

On 3-year follow-up 5 patients died and 10 were lost to follow up. The causes of death were: congestive heart failure [2]; pulmonary tuberculosis [1]; unknown [2]. Among the 55 available for follow up, three had had hospitalization due to stroke, heart failure and deep venous thrombosis (*Table 2*).

Discussion

This study of recently diagnosed HIV-infected ART-naïve individuals showed high occurrence of overweight, hypertension, hyperlipidemia and hyperglycemia, as well as evidence of pro-coagulant state in a considerable proportion of patients. Impaired left ventricular systolic function was present in a quarter of patients, despite only four having overt heart failure. Our results confirm a double burden of disease in this young population from a low-income setting.

STEPS surveys have been implemented in 42 African countries showing high prevalence of risk factors in some (20). In Mozambique high prevalence of cardiovascular risk factors was found in urban settings (16,18), and a rise in prevalence of hypertension from 33.1% to 38.9% (19) occurred over 10 years. The joint burden of HIV and NCD reduces the quality of life and life expectancy of patients, reducing the impact of the 90-90-90 strategy (3).

Despite HIV-infected people in sSA being at risk of CVD due to aging, exposure to infectious agents, direct consequences of HIV and exposure to specific antiretrovirals (23-30), screening for cardiovascular risk factors or diseases is not systematically performed and NCD-HIV integrated programs are scarce (31). A risk of non-AIDS-related mortality exceeding the risk of AIDS-related mortality has been reported among individuals enrolling into care with CD4+ counts greater than 200 cells/mm^3 (32). Our results are in line with estimates pooled from a systematic review of the prevalence of cardiovascular risk factors, which found prevalence of 7.8% (95% CI: 4.3–13.9) for obesity, 21.2% (95% CI: 16.3–27.1) for hypertension, 22.2% (95% CI: 14.7–32.1) for hypercholesterolemia, 27.2% (95% CI: 20.7–34.8) for hypertriglyceridemia and 1.3 to 18% for type-2 diabetes (33).

Our WHO clinical class I-II patients had very low CD4 counts (mean 21.3 cells/mL). A systematic review and meta-analysis of the diagnostic accuracy of this clinical staging system for defining eligibility for ART in sSA revealed that it misses a high proportion of individuals who are ART eligible by CD4 count (34). Thus, because low CD4 count is a strong predictor of thrombotic events in HIV-infected individuals (35,36) and pro-coagulant state favors progression of atherosclerosis, our patients should be considered at higher risk of myocardial infarction, coronary death, ischemic stroke, and peripheral arterial disease (37). The reasons for rise in D-dimers (either related to HIV infection or due to ethnicity factors) need to be clarified in case-control studies matched by ethnic group. Khaleghi and colleagues (38) reported higher levels of D-dimers in African-Americans when compared to other ethnic groups (mean ± SD; men 255±199 *vs.* 190±182 ng/mL, P<0.001; women, 289±233 *vs.* 225±195 ng/mL, P<0.001) in North America; ethnicity remained associated with higher D-dimer levels after adjustment for age, conventional risk factors, medication use and lifestyle variables (38). An Italian cohort of 44 HIV non-smoker adult patients on ART and virally suppressed (10 females and 34 males; mean age 48 years,

mean CD4+ 674 cells/mL) had only 3 patients with high levels of D-dimers (39), despite a lower cut-off for abnormal the value (defined as 250 ng/mL) than the one we used.

Our results suggest that current diagnostic algorithms should be up-graded to include cardiovascular risk screening and stratification of HIV patients undergoing ART. Given the CVD profile in Africa, characterized by low incidence of ischaemic heart disease and high occurrence of hypertensive heart disease, rheumatic heart disease and cardiomyopathies (40), tailored management protocols need to be developed, including referral pathways adapted to local infrastructures and health professionals availability.

After 36 months five out of 70 patients died. Higher early mortality in HIV patients starting ART in sSA, compared to those in Europe and North America, is well documented (7,41). This might be related to infectious comorbidities and lower access to good quality care, but the role of cardiovascular risk factors and the significance of high plasma D-dimers need to be clarified.

Unmeasured environmental risks and poverty may contribute to the pro-coagulant status. In Mozambique, approximately 95% of households burn solid fuels for cooking (42), mostly wood and charcoal. Long- and short-term exposure to air pollution has been related to rise in markers of inflammation and fibrinolysis (43-45), and social disparities determine different exposure to indoor air pollution (45). In a study including 27% of participants of black ethnicity, Hajat *et al.* (43) examined the progression to subclinical and clinical CVD among adults free from disease at baseline, and found a positive association between air pollutants and D-dimer.

We could not perform D-dimers on follow up of our patients. ART has been shown to reduce both D-dimers levels and thromboembolic events. D-dimers steadily decreased from a median level 624 to 214 after 12 months of ART in a cohort of 119 Italian HIV-positive treatment-naïve patients with less than 200 CD4 cells/mL at baseline (46). D-dimers blood levels improvement occurs as soon as 6 months after ART initiation (47). Whether lowering the elevated levels of D-dimer in susceptible population groups by lifestyle or pharmacologic means will lower cardiovascular morbidity and mortality still needs confirmation by randomized controlled trials.

Innovative care delivery models including use of point-of-care diagnostics—such as portable ultrasound and rapid tests for biomarkers we used in this study—may support comprehensive NCD care, by allowing prompt diagnosis and management of comorbidities at peripheral health facilities in resource-limited settings. On the other hand, task-shifting of some specialist competences in cardiovascular care to other health professionals may allow decentralization of care and upgrading of HIV surveillance to include selected NCDs, thus creating integrated NCD-HIV prevention, care, treatment and surveillance models.

While we acknowledge that the results of this descriptive study on patients recruited consecutively in an urban health facility are not generalizable, they raise concern and should call our attention to the urgent need to monitor the occurrence of comorbidities and the trends in risk factors for NCD in HIV-infected individuals. Such efforts are needed to sustain the gains made to reduce the number of lives lost to HIV and to improve quality of life of persons living with HIV, thus contributing to meeting United Nations Sustainable Development Goals in Africa.

Conclusions

High cardiovascular risk was present in HIV-infected ART-naïve patients from a low income setting in sSA, highlighting the need for active CVD screening and training of health professionals for case management at ART initiation in this continent. Research into conventional and geographically relevant risk factors and burden of CVD is warranted to allow tailoring of cardiovascular risk stratification in HIV-infected individuals from this region. This knowledge will be important to effectively plan and organize the chain of services needed to increase patient survival free of major adverse events and to sustain the gains from massive global and local investments on prevention and management of HIV.

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Footnote

Conflicts of Interest: All authors have completed the

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The national bioethics committee approved the study. Informed consent was obtained from all participants.

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