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Results of comprehensive cardiovascular diagnostic work-up in HIV positive patients

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SUMMARY

Cardiovascular disease (CVD) in the HIV population accounts for a large proportion of morbidity and mortality and, with the increased life expectancy, the burden of CVD is expected to rise. Inflammation, immune dysfunction, side effects of HIV medications, high prevalence of other risk factors are the likely pathogenic mechanisms for accelerated atherosclerosis. We aimed to evaluate the diagnostic yield of a cardiovascular multimodality diagnostic work-up in a contemporary cohort of HIV-infected patients. From November 2017 to October 2019, HIV infected patients were screened in a cardiovascular diagnostic work-up program including clinical history, physical examination, arterial blood pressure measurement, 12-lead ECG, and Transthoracic Echocardiogram (TTE). Advanced non-invasive cardiovascular imaging tests, like Coronary Computed Tomography Angiography (CCTA), stress-echocardiography, Cardiac Magnetic Resonance (CMR), were performed in patients with suspicion of chronic coronary syndrome (CCS) or non-ischemic heart disease (NIHD). 117 HIV-infected consecutive patients underwent this cardiovascular diagnostic work-up and were included in our study. Fifty-two patients (45%) had evidence of CVD. Of them, 22 presented Coronary Artery Disease (CAD), whereas 47 cases showed NIHD. In 17 cases both conditions were present. Among patients with CAD, 8 showed critical coronary stenosis; among them, 5 were treated with percutaneous coronary intervention, 2 with Aorto-Coronary By-Pass Grafting (CABG), and one with medical therapy. Hypertension and diabetes were significantly associated with the development of CVD (respectively $p<0.001$ and $p<0.05$), while current smoking ($p<0.02$) and hypertension ($p<0.007$) were positively associated to CAD. A comprehensive cardiovascular diagnostic work-up including advanced multimodality diagnostic imaging modalities led to early detection of CVD in nearly half of an HIV population with immediate interventions required in 6.8% of them, and aggressive prevention treatment started in the remaining HIV patients.

Keywords: HIV, cardiology, multimodality imaging, cardiovascular disease, diagnostic work-up.

INTRODUCTION

The improved prognosis of HIV under the effective antiretroviral regimens increased the interest for other rampant comorbidities responsible for a rising share of the morbidity and mortality observed in these patients [1]. Additionally, in observational studies of HIV patients, the proportion of total deaths due to Cardiovascular Disease (CVD) ranged from 6.5% to 15%, with HIV infection alone conferring a 61% increased risk compared to uninfected individuals of comparable age and sex [1, 2].

The pathophysiology of CVD in HIV is complex

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and multifactorial. The interplay of several items is involved, such as inflammation, autoimmune mechanisms, direct HIV-induced myocardial damage, side effects of HIV medications, nutritional factors, accelerated atherosclerosis and increased burden of traditional cardiovascular risk factors [3-8].

HIV-infected patients can develop both Coronary Artery Disease (CAD), due to accelerated atherosclerosis, and Non-Ischemic Heart Disease (NIHD), since the HIV infection may involve the pericardium, myocardium, cardiac valves and pulmonary circulation [9-24].

The clinical manifestations of CVD in HIV-infected patients differ from the general population, often presenting as unexpected and severe events suddenly interrupting a silent clinical history [25]. A crucial issue is the lack of applicability of conventional risk scores, leaving healthcare providers without reliable decision-making instruments to select the appropriate diagnostic work-up and tailored treatment [26, 27]. Thanks to the recent advances in technology, non-invasive multimodality cardiovascular imaging could be a powerful tool in providing new insights into the pathogenesis of CVD seen in the HIV-positive population and in identifying patients at-risk.

We aimed to evaluate the prevalence of CVD through a cardiovascular multimodality diagnostic investigation in a cohort of HIV-infected patients. We assumed that a thorough diagnostic evaluation would allow to early detection of cardiovascular diseases in a large number of patients, with considerable impact on therapeutic and follow-up strategies.

PATIENTS AND METHODS

Patients selection

This study is a cross-sectional study conducted at the Infectious Diseases outpatient clinic of our tertiary care university hospital. From November 2017 to October 2019, HIV infected patients aged ≥40 years old in follow-up with at least one cardiovascular risk factor such as smoke, hypertension, dyslipidaemia, diabetes were consecutively

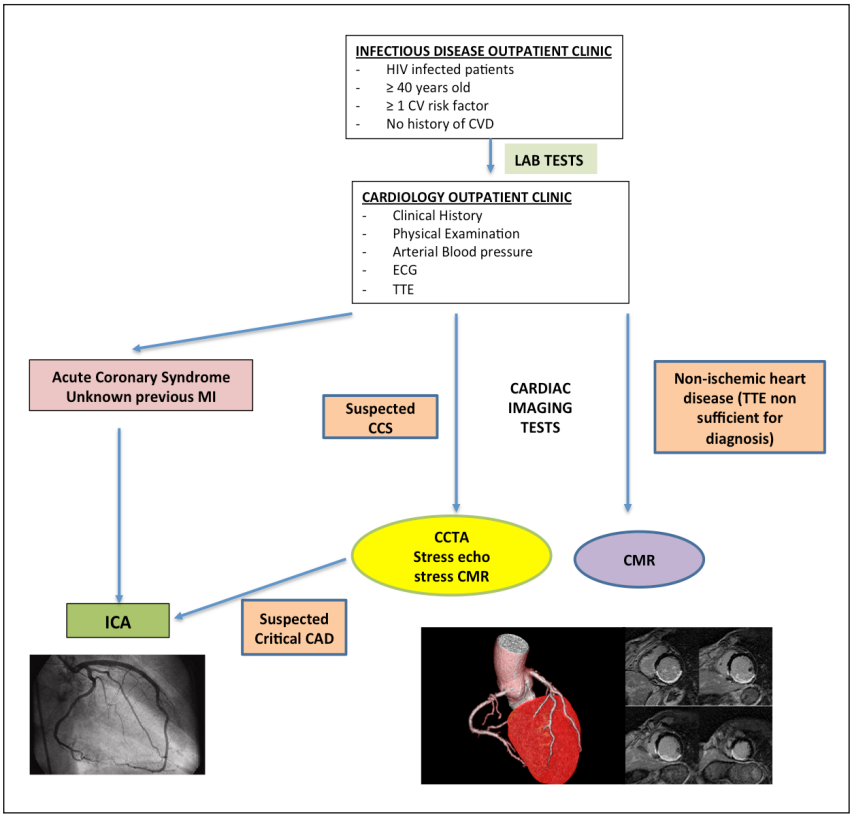

Figure 1 - Diagnostic flow chart of the cardiovascular screening algorithm.
TTE, transthoracic echocardiogram; CAD, coronary artery disease; CMR, cardiac magnetic resonance; CCS, chronic coronary syndrome; MI, myocardial infarction; ICA, invasive coronary angiogram.

enrolled and addressed to the cardiovascular diagnostic work-up program (Diagnostic Flow-chart, Figure 1). All patients provided written informed consent. We excluded from the study patients with a known cardiac disease or those who have not given informed consent.

The viro-immunological profile of each patient has been examined, focusing on HIV duration, duration of antiretroviral therapy (ART) use, CD4+ nadir, zenith viremia, and the presence of detectable viremia. Likewise, we searched for other co-infections (HBsAg positivity, anti-HBc positivity, HCV co-infection) and recorded the antiretroviral therapy administered. The ongoing three drugs ART regimens at the time of the cardiologic visit were divided by the anchor drugs as follows: reverse transcriptase-inhibitor (NNRTI), protease inhibitor (PI), and integrase strand transfer inhibitor (INSTI). Where this definition was not applicable (three-drugs regimen with 1 or 3 nucleoside/nucleotide reverse transcriptase inhibitors [NtRTI/NsRTI], not boosted PI, PI monotherapy and more or less than three drugs) we classified as "others". The panel of laboratory tests included general blood tests like full blood count, glycemia, HbA1c, renal and hepatic function, and lipid profile were collected within 3 months before the cardiology visit.

Cardiovascular diagnostic work-up

HIV-infected patients enrolled in the study were referred to the outpatient Cardiology clinic for a comprehensive cardiology evaluation with the following routine data collection:

- Clinical history and physical examination.
- Arterial blood pressure measurement.
- 12-lead ECG.
- Transthoracic echocardiogram (TTE).

Clinical characteristics, laboratory test results and pharmacological therapy data were collected to assess the Framingham Risk Score, calculated with the software elaborated by CHIP (Centre for Health & Infectious Disease Research) of the Copenaghen University.

According to the diagnostic flow-chart (Figure 1), patients presenting clinical, ECG, and/or echocardiographic features of unstable angina or with evidence of previous silent myocardial infarction were admitted to hospital to perform an invasive coronary angiogram (ICA). Patients with clinical, ECG, and/or echocardiographic features suggestive for a chronic coronary syndrome (CCS) underwent a second-level non-invasive imaging test (coronary computed tomography angiography (CCTA) and/or stress echocardiography/stress cardiac MRI) [28]. Whether critical CAD was suspected (coronary stenosis >50% at the CCTA examination and/or positive stress echocardiogram/MRI), hospital admission was scheduled to perform ICA. Patients with evidence of cardiomyopathy, moderate-to-severe valvular disease not properly assessable by TTE, or with pericardial effusion underwent Cardiac Magnetic Resonance. Counseling for lifestyle modification and smoking cessation was offered to all patients with modifiable cardiovascular risk factors. The baseline therapy of all patients was carefully evaluated and modified, if necessary, based on the current European guidelines on CVD prevention [29] and after careful verification of any drug interactions with the ongoing antiretroviral therapy, through consultation of the reference tabs drafted by the University of Liverpool (https://www.hiv-druginteractions.org/).

Patients with evidence of cardiovascular disease, intended as any clinical condition involving heart, great vessels and coronary arteries requiring treatment changes were included in a tailored follow-up program.

CAD was defined as the evidence of ≥1 coronary plaques at the CCTA or ICA examination. Critical CAD was defined as coronary stenosis ≥75% in ≥1 vessels (≥50% in the left main coronary artery) at the ICA. Liberal use of intracoronary physiologic measurements was encouraged when required.

Statistical analysis

Continuous variables were expressed as mean (M) ± standard deviation (SD) when normally distributed or as median and interquartile range (IQR) when not normally distributed. Categorical variables were expressed as number (N) and percentage (%). The Student 2-sample t-test and Mann-Whitney-Wilcoxon rank-sum test were used to compare the differences between groups for continuous variables. X^2 and Fisher exact test were used for categorical variables where appropriate. All statistical analyses were performed using a standard software package (Stata, version 14.0; StataCorp). Two-sided probability values were considered significant at $p<0.05$.

RESULTS

Basic features of the investigated population

One hundred and fifty HIV-infected patients older than 40 years of age have been referred for cardiovascular diagnostic work-up. Of those, 117 patients met the inclusion criteria.

The baseline characteristics of the investigated population are summarized in Table 1.

Of the patients evaluated, 91 were males (77.7%) and 26 females (22.3%). The mean age was 56 years. The most frequent transmission route resulted the sexual one: heterosexuals in 50.4% of cases, and omosexuals in 36.8% (males who have sex with males (MSM). The 7.7% were intravenous drug user, and the 5.1% of patients were illicit drugs abusers, or alcohol.

The viro-immunologic characteristics at baseline of the population are listed in Table 2. The median of years of positivity to HIV was 21 (range 0-34), while the median of ART treatment was 19 years [IQR 11-22]. The 91.2 % of patiens had no detectable viremia (<20 copies/mL) in plasma. The co-infections recorded were 9.8% HBV, 18.6% HCV and 23.5% syphilis. The 14.7% of patients had a previous AIDS event, and 5.9% had an acute retroviral infection. As for ART, the Integrase Strand Transfer Inhibitors (INSTI) were the most used anchor drug (53%). As shown in Table 3, 50% of patients had less than two comorbidities, 32.3% had between 3 and 4, and 17.7% had more than four comorbidities. Table 4 lists the cardiovascular (CV) risk factors, baseline therapy, arterial blood pressure, and ECG interpretation. Among the patients, the 53% had dyslipidemia, the 47% were current smokers, the 37% suffered from hy-

Table 1 - Demographic characteristics.

Demographic characteristics, n=117 (%)	
Age (years)	56 ± 9
Sex	
Female	26 (22.2%)
Male	91 (77.7%)
Risk	
Heterosexual	59 (50.4%)
MSM	43 (36.8%)
IVDU	9 (7.7%)
other	6 (5.1%)
Ethnicity	
Caucasic	102 (87.2%)
African	6 (5.1%)
Hispanic	5 (4.3%)
Middle-Eastern	2 (1.7%)
African-American	1 (0.9%)
South-Est Asiatic	1 (0.9%)

MSM, male who has sex with male; IVDU, intravenous drug user.

Table 2 - Viro-immunologic characteristics.

Viro-immunologic characteristics	*n=117*
Duration HIV (years, median, IQR)	21, 13-26
Duration ART use (years, median, IQR)	19, 11-22
Nadir CD4+ (cells/µL), median, IQR	251, 159-332
Zenith viremia (copie/mL), median, IQR	60000, 7000-207000
Drug abuse	6 (5.1%)
Alcohol Abuse	6 (5.1%)
Detectable viremia	9 (7.7%)
HBsAg positivity	10 (8.5%)
anti-HBc positivity	32 (27.3%)
HCV co-infection	19 (16.2%)
Syphilis	24 (20.5%)
Previous AIDS event	15 (12.8%)
Acute retroviral infection	6 (5.1%)
Single tablet regimen	51 (43.5%)
Previous exposure to abacavir	44 (37.6%)
Last therapy INSTI NNRTI PI NRTI Others	 53% 24% 3% 1% 19%

ART, antiretroviral therapy; PI, protease inhibitors; NRTI, Nucleoside analogue reverse-transcriptase inhibitors; INSTI, Integrase strand transfer inhibitors; NNRTI, non-nucleoside analogue reverse-transcriptase inhibitors; IQR, Interquartile Range.

Table 3 - Charlson Comorbidity index.

Score	
<2	50%
3-4	32.7%
>4	17.4%

pertension, and the 9% were diabetic. Of note, 29.1% of them presented a single CV risk factors, whereas the 27.3% presented ≥3 CV risk factors.

Results of the cardiovascular diagnostic work-up

Of the 117 patients evaluated in the study, one patient showed ECG and TTE findings of previous silent myocardial infarction, and another one had features of unstable angina; both were hospitalized with high priority to perform an ICA.

Table 4 - Results from cardiology visit.

Cardiovascular risk factors	*n=117*
Smoke (current)	55 (47%)
Smoke (previous)	31 (26.5%)
Hypertension	43 (36.8%)
Diabetes	11 (9.4%)
Dyslipidemia	62 (53%)
Family history of CAD	27 (23.1%)
1 CV risk factor	34 (29.1%)
2 CV risk factors	45 (38.5%)
≥3 CV risk factors	32 (27.3%)
Framingham risk score	16.7±12.9
Baseline therapy	
Statins	19 (16.5%)
Ezetimibe	3 (2.6%)
Fibrates	3 (2.6%)
Diuretics	10 (8.7%)
Ca-antagonists	13 (11.3%)
ACE-I	19 (16.5%)
ARBs	11 (9.6%)
Alfa-blockers	3 (2.6%)
Beta Blockers	10 (8.5%)
Arterial blood pressure	
SBP (mmHg)	135, 121-143.5
DBP (mmHg)	80, 75-89
MAP(mmHg)	97, 90-106
ECG	
Sinus rythm	116 (99.1%)
Atrial fibrillation	1 (0.09%)
Heart rate (bpm)	74±13

CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; ACE-I, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

Non-invasive second level imaging test was performed in 27 patients with suspected CCS. CCTA was performed in 24 patients and stress-echocardiography or cardiac MRI with dipyridamole was performed in 3 patients. Nine of them underwent ICA in the suspicion of critical CAD. Nine patients with evidence of NIHD underwent CMR.

Prevalence of cardiac disease

Of the 117 patients evaluated in the screening, 52 (45%) had evidence of cardiovascular disease (Table 5). Of them, 22 presented CAD, whereas 47 cases showed a NIHD. In 17 cases both conditions were present.

ICA confirmed a critical CAD in 8 patients: 5 of them were treated with percutaneous coronary interventions, 2 with aorto-coronary by-pass (CABG), one presented a chronic coronary occlusion with non-viable myocardium and remained on medical treatment. Three patients undergoing ICA and 11 patients assessed non-invasively with CCTA showed a non-critical CAD requiring medical therapy and follow-up. Among the 8 patients with critical CAD, 4 were asymptomatic, 2 reported atypical chest pain, and 2 complained of exertional dyspnoea.

The NIHD group was broader and more heterogeneous. Hypertensive cardiomyopathy was the

Table 5 - Results of the diagnostic work-up: prevalence of the cardiovascular disease.

Prevalence of CVD	*n=117*
CVD	52 (44%)
Coronary artery disease	22 (18.8%)
Critical coronary artery disease	8 (6.8%)
Non-critical CAD	14 (11.9%)
Non-ischemic heart disease	47 (40.1%)
Hypertensive cardiomyopathy	21 (17.9%)
Aortic disease	9 (7.7%)
Pericardial effusion	5 (4.3%)
Valvular disease (moderate-to-severe degree)	14 (11.9%)
Atrial fibrillation	1 (0.8%)
Hypertrophic cardiomyopathy	2 (1.7%)
Pulmonary hypertension	5 (4.3%)
LV systolic dysfunction	3 (2.6%)

CVD, cardiovascular disease; CAD, coronary artery disease; LV, left ventricle.

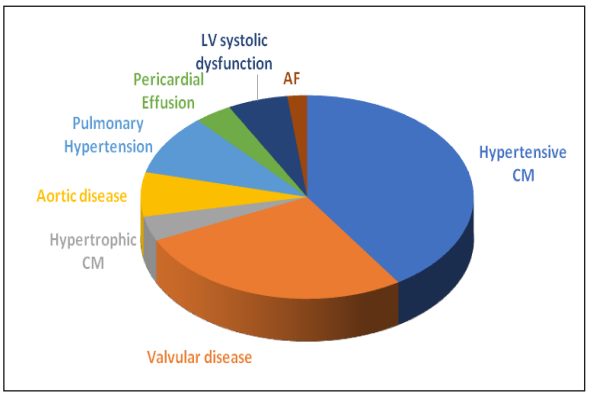

Figure 2 - Non-ischemic heart disease in the population examined.
LV, left ventricle; CM, cardiomyopathy; AF, atrial fibrillation.

most frequent condition, with 21 cases diagnosed (18%). The 12% of patients showed valvular disease of moderate or severe degree and the 8% expressed thoracic aortic dilatation (>40 mm). Pericardial effusion, pulmonary hypertension, and left ventricle (LV) systolic dysfunction were also found in some patients (Table 5, Figure 2). Two cases of hypertrophic cardiomyopathy and one patient with atrial fibrillation were also detected.

Risk of CVD

As reported in Table 6, patients with CVD were older than those without CVD (60.7±8.8 vs 53.4±7.3; $p<0.001$). Hypertension and diabetes were significantly associated with the development of CVD ($p<0.001$ and $p<0.05$, respectively), whereas smoking and dyslipidaemia did not show a significant association. Patients with higher levels of blood pressure at the visit and of glucose at the laboratory exams had an increased risk of CVD. The duration of HIV infection, the presence of detectable viremia and the impact of the last therapy on the CVD prevalence were not significantly associated with the development of CVD.

Risk of CAD

As for the CVD group, patients with CAD were older with a mean age of 60.2±7.0 years, compared to the 56.4±9.1 shown by the patients without CAD (p=0,049, Table 7). In the development of CAD, gender demonstrated to be statistically significant as all patients with CAD were male (p=0.007). Current smoking was positively associ-

Table 6 - Univariate analysis: CVD vs. no-CVD.

	CVD n=52	*no CVD n=50*	*p value*
Age (years)	60.7±8.8	53.4±7.3	<0.001
Males	43 (82.7%)	37 (74%)	0.286
Females	9 (17.3%)	13 (26%)	0.286
Detectable viremia (<20 copies/mL)	5 (9.6%)	4 (8%)	0.77
Duration HIV (years)	20.3±7.5	20.1±7.5	0.55
Duration ART use <10 years >10 years	 11 (21.2%) 41 (78.6%)	 11 (22%) 39 (78%)	 0.917 0.917
Last therapy INSTI NNRTI PI NRTI	 24 11 2 1	 21 13 1 0	0.194
Smoke (current)	25 (48%)	20 (40%)	0.362
Smoke (previous)	13 (25.5%)	15 (30%)	0.613
Hypertension	27 (53%)	10 (20%)	0.001
Diabetes	8 (15.7%)	2 (4%)	0.049
Dyslipidemia	30 (58.8%)	23 (46%)	0.197
SBP (mmHg)	140±17	128±14	<0.001
DBP (mmHg)	83±11	78±10	0.02
MAP (mmHg)	100±19	92±13	0.02
White blood cells (109/L)	6393±2003	6675±2013	0.48
HbA1c (mmol/mol)	39±12	38±7	0.56
Glucose(mg/dL)	109±37	94±14	0.01
Col Tot (mg/dL)	196±37	201±35	0.5
LDL (mg/dL)	117±40	119±36	0.84
HDL (mg/dL)	53±23	48±16	0.2
Tg (mg/dL)	168±117	173±167	0.87
Lp(a)	285±385	312±411	0.71
NT-proBNP	91±111	77±85	0.49
hs-CRP (mg/L)	90±111	77±85	0.52

CVD, cardiovascular disease; ART, antiretroviral therapy; PI, protease inhibitors; NRTI, nucleoside analogue reverse-transcriptase inhibitors; INSTI, integrase strand transfer inhibitors; NNRTI, non-nucleoside analogue reverse-transcriptase inhibitors; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HbA1c, Glycated hemoglobin; Lp(a), lipoprotein(a); NT-proBNP, N-terminal prohormone of brain natriuretic peptide; LDL, low-density lipoprotein; Tg, triglycerides; hs-CRP, high sensitivity C-reactive protein.

Table 7 - Univariate analysis: CAD vs. no-CAD.

	CAD n=22	*no-CAD n=80*	*p value*
Age (years)	60.2±7	56.4±9.1	0.049
Males	22 (100%)	59 (73.7%)	0.007
Females	0 (0%)	22 (27%)	0.007
Detectable viremia	3 (13.6%)	6 (7.5%)	0.77
Duration HIV (years)	21±7.5	19.9±7.6	0.444
Duration ART use (years)			
<10	3 (13.6%)	19 (23.7%)	0.363
>10	18 (81.8%)	62 (77.5%)	0.363
Last therapy INSTI NNRTI PI NRTI	 11 5 1 0	 44 19 2 1	0.970
Smoke (current)	14 (63.6%)	31 (38.7%)	0.02
Smoke (previous)	3 (13.6%)	25 (31.3%)	0.122
Hypertension	13 (59.1%)	24 (30%)	0.007
Diabetes	4 (18.2%)	6 (7.5%)	0.115
Dyslipidemia	10 (45.5%)	43 (53.8%)	0.617
SBP (mmHg)	144.7±18.6	131.5±15.7	0.003
DBP (mmHg)	87±11	79±10	0.006
MAP (mmHg)	106±13	93±19	0.007
White blood cells (10^9/L)	6955±2218	6421±1943	0.278
Glucose (mg/dL)	116±44	98±23	0.0196
HbA1c (mmol/mol)	44±18	37±6	0.012
Col Tot (mg/dL)	189±34	201±36	0.187
LDL (mg/dL)	115±35	119±39	0.731
HDL (mg/dL)	54±13	52±21	0.088
Tg (mg/dL)	174±117	170±149	0.894
Lp(a)	267±278	306±380	0.67
ntProBNP	80.5±109	85.4±97	0.8437
hsPCR (mg/L)	78.3±110	85.4±97	0.777

CVD, cardiovascular disease; ART, antiretroviral therapy; PI, protease inhibitors; NRTI, nucleoside analogue reverse-transcriptase inhibitors; INSTI, integrase strand transfer inhibitors; NNRTI, non-nucleoside analogue reverse-transcriptase inhibitors; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HbA1c, glycated hemoglobin; Lp(a), lipoprotein(a); NT-proBNP, N-terminal prohormone of brain natriuretic peptide; LDL, low-density lipoprotein; Tg, triglycerides; hs-CRP, high sensitivity C-reactive protein.

Table 8 - Framingham risk score of patients with CAD vs. patients with no CAD.

Framingham risk score	*CAD*	*no-CAD*	*p-value*
<10%	17.7%	40.6%	0.161
10-20%	29.4%	26.7%	
>20%	53%	32.4%	

CAD, coronary artery disease

ated to CAD (66.7% vs 38.0%; p=0.02), as well as hypertension (62% vs 30% p=0.007). Although the blood glucose and HbA1c level were higher in CAD group than in the group without CAD, the prevalence of known DM among patients with CAD was higher but not statistically significant when compared with the group without CAD (p=0,115). The lipid profile did not differ significantly in the two groups, with patients affected by CAD presenting even lower total cholesterol, LDL, triglycerides, and higher HDL levels compared to patients without CAD (Table 7).

The Framingham score was unable to perform a correct risk stratification of CAD in our population (Table 8).

DISCUSSION

The HIV infection alone appears to confer a 61% increased risk for cardiovascular disease compared with the general population [2, 30]. Furthermore, the prolongation of life expectancy in the past two decades obtained with the introduction of cART means that HIV-infected people have been affected by more comorbidities and age-related non-communicable diseases. The pathogenic mechanisms underlying CVD in HIV-infected patients are still debated and risk stratification tools to predict the risk in this population are lacking [31]. The current study shows a surprisingly high prevalence of CVD in HIV-infected patients >40 years old with at least one CV risk factor. Of the 117 patients enrolled in our study, 45% showed a cardiovascular disease. Of note, 10% of the cohort examined required hospitalization to perform ICA in the suspicion of critical CAD, which was confirmed in 8 patients out of 11.

Importantly, none of these patients presented with typical chest pain, and half of them were completely asymptomatic. It is important to perform a comprehensive cardiac evaluation in all

HIV patients at increased cardiovascular risk, even if they do not complain of typical symptoms for CAD, to unmask silent but potentially life-threatening cardiac conditions.

The algorithm that we applied for the diagnosis of CCS followed the current European guidelines recommending either non-invasive anatomical imaging using CCTA or functional imaging as the initial test to rule out or establish the diagnosis of CCS in high-risk patients [28]. In non-HIV patients, CCTA demonstrated strong prognostic value in patients with suspected CAD. The Prospective Studies PROMISE and SCOT-HEART have shown the incremental value of CCTA over the conventional practice in investigating patients with suspected angina [32]. Moreover, technological developments have also led to a marked reduction in radiation dose. Imaging with most recent dedicated CT scanners can be performed with low (3-5 mSv) and ultra-low (<1 mSv) radiation doses [33]. Non-invasive functional imaging such as stress echocardiography or stress CMR is an alternative to CCTA in the diagnosis of myocardial ischemia, and it is recommended if coronary CTA has shown CAD of uncertain functional significance or is not diagnostic. Although exercise-ECG was the most widely used provocative test in clinical practice, recent guidelines have downgraded its indication due to its low sensitivity, moderate specificity, and frequent equivocal results. For these reasons, exercise ECG was avoided in a population at high risk of CV events as the HIV one due to its low accuracy. In contrast, non-invasive advanced imaging modalities such as CCTA were extensively applied in patients with suspicion of CCS. The benefit is not only to diagnose flow-limiting CAD but also to detect non-obstructive CAD and thus to identify patients who could benefit from aggressive preventive medications (*i.e.*, aspirin or statins) and lifestyle interventions. This allowed us to limit invasive angiography to a small minority of patients, with angiography confirming in most of them severe coronary artery disease.

Non-ischemic heart disease was frequent in our population, with an overall prevalence of 40.1%, and included a heterogeneous cluster of conditions, with hypertensive heart disease being the most frequent.

Similarly to the general population, hypertension appears to play an essential role in the development of CVD also for our HIV patients. It is of clinical relevance that a Systolic Blood Pressure (SBP) mean value overcoming slightly the target for treatment established by the EACS guidelines (SBP<140), was found both in the group with evidence of CVD (140±17; p<0,001) and in the subgroup with CAD (144±18; p=0,007) [34]. As for Diastolic Blood Pressure (DBP), the mean values remained under the target for both groups (DBP<90). There is no tailored guideline for hypertension treatment in HIV patients, forcing physicians to adopt the same approach applied to the general population. However, this data suggests that BP targets may be lowered in HIV patients such as in other high-risk patients such as those with diabetes, starting lifestyle modifications and drug interventions as soon as BP exceeds the upper range of normal.

In our study, patients with CVD, and particularly those with CAD, showed an increased prevalence of glucose metabolism disorders. Conversely, we did not find any significant association between CVD and the alteration of the lipid profile. In fact, despite a high prevalence of dyslipidaemia in the whole study group (51.9%), higher (58,8%) among those who had CVD, these findings were not supported by statistical significance.

Our study is in line with previous reports concerning the current smoking habit, which appeared strongly associated with the development of CAD. These results confirmed the importance of counseling for quitting the smoking habit in this high-risk group of patients.

The population we examined was well treated for their HIV infection, presenting a detectable viremia (>20 copies/μL) only in 9.6% of patients. The same prevalence was found in the group with CVD, regardless of the time of infection and ART treatment. This data is similar to other studies, where it has already been clarified the emerging role of inflammation and immune activation as drivers of comorbidities, despite an optimal control of viremia and CD4+ T cells level [35, 36].

The Framingham score was unable to stratify the cardiovascular risk in our population, confirming, as previous studies stated, the need for a specific cardiovascular risk score tailored for HIV patients [37, 38].

The principal limitation of this study regards the small dimension of the investigation as well as the lack of longitudinal follow-up data, which

could evaluate the significant benefit in terms of survival and reduction of major adverse cardiovascular events caused by the application of the diagnostic and therapeutic algorithms applied in this study. Moreover, a match with an HIV-negative control group is welcome to evaluate differences in the prevalence of CVD in comparable cohorts.

CONCLUSION

A comprehensive cardiovascular diagnostic work-up, including new advanced multimodality diagnostic imaging modalities, demonstrated to be a useful tool to ensure early diagnosis and better management of CVD in HIV patients.
Our study proved that a standardized cardiology evaluation is necessary, particularly in a subset of patients in which CVD does not manifest with its traditional signs and symptoms. The early recognition of cardiovascular disease allows prompt management of symptoms and, through the strict control of cardiovascular risk factors, we can modify the natural course of cardiovascular disease in HIV patients.

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None

REFERENCES

[1] Stein JH, Hsue PY. Inflammation, immune activation and CVD risk in individuals with HIV infection. *JAMA.* 2012; 308 (4), 405-6.
[2] Boccara F, Lang S, Meuleman C, et al. HIV and coronary heart disease time for a better understanding. *J Am Coll Cardiol.* 2013; 61 (5), 511-23.
[3] Younas M, Psomas C, Reynes J, Corbeau P. Immune activation in the course of HIV-1 infection: Causes, phenotypes and persistence under therapy. *HIV Med.* 2016; 17 (2), 89-105.
[4]Herskowitz A, Wu TC, Willoughby SB, et al. Myocarditis and cardiotropic viral infection associated with severe left ventricular dysfunction in late-stage infection with human immunodeficiency virus. *J Am Coll Cardiol.* 1994; 24 (4), 1025-32.
[5] Hileman CO, Funderburg NT. Inflammation, immune activation and antiretroviral therapy in HIV. *Curr HIV/AIDS Rep.* 2017; 14 (3), 93-100.
[6] Kearns A, Gordon J, Burdo TH, Qin X. HIV-1–associated atherosclerosis: unraveling the missing link. *J Am Coll Cardiol. 2017*; 69 (25), 3084-98.
[7] Wu M, Li C, Hou MF, Chu PY. New insights into the role of inflammation in the pathogenesis of atherosclerosis. *Int J Mol Sci.* 2017; 18 (10), 2034.
[8] Nguyen MT, Fernando S, Schwarz N, Tan JTM, Bursill CA, Psaltis PJ. Inflammation as a therapeutic target in atherosclerosis. *J Clin Med.* 2019; 8 (8), 1109.
[9] Vachiat A, McCutcheon K, Tsabedze N, Zachariah D, Manga P. HIV and ischemic heart disease. *J Am Coll Cardiol.* 2017; 69 (1), 73-82.
[10] Triant VA, Grinspoon SK. Epidemiology of ischemic heart disease in HIV. *Curr Opin HIV AIDS.* 2017; 12 (6), 540-7.
[11] Hemkens LG, Bucher HC. HIV infection and cardiovascular disease. *Eur Heart J.* 2014; 35 (21), 1373-81.
[12] Freiberg MS, So-Armah K. HIV and cardiovascular disease: We need a mechanism, and we need a plan. *J Am Heart Assoc.* 2016; 4 (3), e003411.
[13] Manga P, McCutcheon K, Tsabedze N, Vachiat A, Zachariah D. HIV and nonischemic heart disease. *J Am Coll Cardiol.* 2017; 69 (1), 83-91.
[14] Reuter H, Burgess LJ, Doubell AF. Epidemiology of pericardial effusions at a large academic hospital in South Africa. *Epidemiol Infect.* 2005; 133 (3), 393-9.
[15] Heidenreich PA, Eisenberg MJ, Kee LL, et al. Pericardial effusion in AIDS: Incidence and survival. *Circulation.* 1995; 92 (11), 3229-34.
[16] Imazio M, Adler Y. Management of pericardial effusion. *Eur Heart J.* 2013; 34 (16), 1186-97.
[17] Ntusi N, O'Dwyer E, Dorrell L, et al. HIV-1-Related cardiovascular disease is associated with chronic inflammation, frequent pericardial effusions, and probable myocardial edema. *Circ Cardiovasc Imaging.* 2016; 9 (3), e004430.
[18] Remick J, Georgiopoulou V, Marti C, et al. Heart failure in patients with human immunodeficiency virus infection: Epidemiology, pathophysiology, treatment, and future research. *Circulation.* 2014; 129 (17), 1781-9.
[19] Savvoulidis P, Butler J, Kalogeropoulos A . Cardiomyopathy and heart failure in patients with HIV infection. *Can J Cardiol.* 2019; 35 (3), 299-309.
[20] Reinsch N, Esser S, Gelbrich G, et al. Valvular manifestations of human immunodeficiency virus infection-results from the prospective, multicenter HIV-HEART study. *J Cardiovasc Med (Hagerstown*). 2013 Oct; 14 (10), 733-9.
[21] Speich R, Jenni R, Opravil M, Pfab M, Russi EW. Primary pulmonary hypertension in HIV infection. *Chest.* 1991; 100 (5), 1268-71.
[22] Basyal B, Jarrett H, Barnett CF. Pulmonary Hypertension in HIV. *Can J Cardiol.* 2019; 35 (3), 288-98.
[23] Degano B, Guillaume M, Savale L, et al. HIV-associated pulmonary arterial hypertension: Survival and prognostic factors in the modern therapeutic era. *AIDS.* 2010; 24 (1), 67-75.

[24] Humbert M, Sitbon O, Chaouat A, et al. Pulmonary arterial hypertension in France. Results from a National Registry. *Am J Respir Crit Care Med.* 2006; 173 (9), 1023-30.
[25] Mondy KE, Gottdiener J, Overton ET, et al. High prevalence of echocardiographic abnormalities among HIV-infected persons in the era of highly active antiretroviral therapy. *Clin Infect Dis.* 2011; 52 (3), 378-86.
[26] Triant VA, Perez J, Regan S, et al. Cardiovascular risk prediction functions underestimate risk in HIV infection. *Circulation.* 2018; 137 (21), 2203-14.
[27] Feinstein MJ, Hsue PY, Benjamin LA, et al. Characteristics, prevention, and management of cardiovascular disease in people living with HIV: a scientific statement from the American Heart Association. *Circulation.* 2019; 140 (2), e98-e124.
[28] Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J.* 2020; 41 (3), 407-77.
[29] Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J.* 2016; 37 (29), 2315-81.
[30] Shah ASV, Stelzle D, Ken Lee K, et al. Global burden of atherosclerotic cardiovascular disease in people living with HIV systematic review and meta-analysis. *Circulation.* 2018; 138 (11), 1100-12.
[31] Feinstein MJ, Bogorodskaya M, Bloomfield GS, et al. Cardiovascular complications of HIV in endemic countries. *Curr Cardiol Rep.* 2016; 18 (11), 113.
[32] Fordyce CB, Newby DE, Douglas PS. Diagnostic Strategies for the evaluation of chest pain: Clinical implications from SCOT-HEART and PROMISE. *J Am Coll Cardiol.* 2016; 67 (7), 843-52.
[33] Fuchs TA, Stehli J, Bull S, et al. Coronary computed tomography angiography with model-based iterative reconstruction using a radiation exposure similar to chest X-ray examination. *Eur Heart J.* 2014; 35 (17), 1131-6.
[34] EACS (European AIDS Clinical Society) guidelines; Version 10.0, 2019. Available at: https://www.eacsociety.org [accessed 15 December 2019].
[35] Schouten J, Wit FW, Stolte IG, et al. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: The AGEhIV Cohort Study. *Clin Infect Dis.* 2014; 59 (12), 1787-97.
[36] Lederman MM, Funderburg NT, Sekaly RP, Klatt NR, Hunt PW. Residual immune dysregulation syndrome in treated HIV infection. *Adv Immunol.* 2013; 119, 51-83.
[37] Dufouil C, Beiser A, Mclure LA, et al. A revised Framingham stroke risk profile to reflect temporal trends. *Circulation.* 2017, 135 (12), 1145-59.
[38] Freiberg MS, Chang CCH, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med.* 2013; 173 (8), 614-22.