Fattori di rischio cardiovascolare negli individui che vivono con HIV: uno studio osservazionale retrospettivo monocentrico.

Cardiovascular risk factors in People Living With HIV: a single centre retrospective observational study.

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Riassunto

Le patologie non-AIDS-definenti sono una sfida emergente, in particolare le patologie cardiovascolari, grazie all'incremento dell'aspettativa di vita degli individui che vivono con HIV (PLWH). Scopo del lavoro è descrivere la prevalenza dei fattori di rischio cardiovascolare e investigare i predittori di ipertensione arteriosa, dislipidemia e diabete mellito tipo II nei PLWH. È stato condotto uno studio retrospettivo cross-sectional analizzando i dati dei PLWH seguiti presso l'UOC di Malattie Infettive dell'Azienda Ospedaliera Universitaria Senese nel 2020-2021.

Sono stati arruolati 286 PLWH: 70% maschi, età mediana 54,4 interquartile range (IQR) 46,8-59,5, 33% fumatori, con un tempo mediano dalla diagnosi di 14,7 anni IQR 8,1-24,9. Il 56,6% era dislipidemico, il 37,8% iperteso e il 7% diabetico. Nove (3%) avevano avuto almeno un evento cardiovascolare maggiore. All'analisi logistica multivariata la dislipidemia è risultata associata ad ipertensione arteriosa (adjusted odds ratio, aOR 2,21, intervallo di confidenza, IC, 95% 1,25-3,88, p=0,006), precedente esposizione a inibitori della proteasi (PIs) (aOR 2,08, IC 95% 1,21-3,58, p=0,008), HIV-RNA rilevabile (aOR 1,90, IC 95% 1,11-3,26, p=0,019) ed età ≥50 anni (aOR 1,93, IC 95% 1,10-3,39, p=0,021). L' ipertensione arteriosa è risultata associata a dislipidemia (aOR 2.87, IC 95% 1.52-5.44, p<0.001), età ≥50 anni (aOR 2.62, IC 95% 1.31-5.23, p=0.006) e BMI >30 kg/m^2 (aOR 5,18, IC 95% 2,17-12,38, p<0,001). Il diabete mellito di tipo II è risultato associato all'ipertensione arteriosa (aOR 3.65, IC 95% 1.07-12.44, p=0.039).

Nei PLWH elevato BMI, età, alterazioni pressorie, lipidiche e glucidiche coesistono con esposizione a PIs e viremia rilevabile quali fattori di rischio per dislipidemia, ipertensione e diabete mellito.

Abstract

Non-AIDS-defining Illnesses are a rising challenge, foremost cardiovascular disease thanks to increase of the life expectancy of People Living With HIV (PLWH). Our aim was to describe the prevalence of cardiovascular risk factors and investigate predictors of blood hypertension, dyslipidemia, and diabetes mellitus type II in PLWH population. We conducted a retrospective cross-sectional study including PLWH followed in the Infectious Diseases Unit of Azienda Ospedaliera Universitaria Senese in 2020-2021.

Two-hundred and eighty-six PLWH were enrolled: 70% males, median age 54.4 interquartile range (IQR) 46.8-59.5, 33% smokers, with a median seropositive time of 14.7 years IQR 8.1-24.9. Among those 56.6% had dyslipidaemia, 37.8% hypertension and 7% diabetes mellitus. Nine (3%) PLWH had experienced of at least one major cardiovascular event. At multivariate logistic analysis blood hypertension (adjusted odds ratio, aOR 2.21, 95% confidence interval, CI 1.25-3.88, p=0.006), previous protease inhibitors (PIs) exposure (aOR 2.08, 95%CI 1.21-3.58, p=0.008), detectable HIV-RNA (aOR 1.90, 95%CI 1.11-3.26, p=0.019) and age ≥50 years (aOR 1.93, 95%CI 1.10-3.39, p=0.021) were associated with dyslipidaemia. Dyslipidaemia (aOR 2.87, 95%CI 1.52-5.44, p<0.001), age ≥50 years (aOR 2.62, 95%CI 1.31-5.23, p=0.006) and BMI >30 kg/m^2 (aOR 5.18, 95%CI 2.17- 12.38, p<0.001) were associated with blood hypertension. Blood hypertension was associated with diabetes mellitus type II (aOR 3.65, 95%CI 1.07-12.44, p=0.039). In PLWH high BMI, age, blood pressure, lipid and glucose alterations coexist with exposure to PIs and detectable viraemia as risk factors for dyslipidemia, hypertension and diabetes mellitus.

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Introduction

Nowadays due to increasing widespread availability of effective and well-tolerated combined antiretroviral therapy (cART), survival and quality of life in people living with HIV (PLWH) significantly improved. The increasing subset of older adults has a burden of non-communicable diseases (NCDs) similar to the general population but with a higher risk of age-related NCDs (1). Indeed, PLWH have an excess risk of cardiovascular disease (CVD) than people without HIV (2) with a driving mechanism that includes traditional and non-traditional risk factors (CVRF) (3). Non-traditional risk factors specific for PLWH included cART related mechanisms, affecting body weight and lipidic metabolism (4), although current therapies are less directly toxic than in early cART, and virus-related mechanisms (5), including pro-inflammatory status, CD4+ T-cell depletion, alteration of cholesterol metabolism and intestinal disorders. The traditional risk factors assumed peculiar patterns and epidemiology among PLWH and include smoking (6), body weight, familiarity, ageing (1), arterial hypertension (7), dyslipidemia (8) and diabetes mellitus type II (DM II) (9). In recent years many studies focused on the best predictive score to assess the risk of CVD. Researchers found that traditional risk charts designed for general population can underestimate the risk in PLWH (10) and lack specific scores designed in this setting (11). The burden of NCDs, especially CVD, directly affects morbidity, mortality, costs and needs to be investigated due to design a multi-disciplinary patient management for an early diagnosis and treatment of CVRF (12) including primary prevention strategies using lifestyle intervention and therapies (13; 14). Our study aims to describe the prevalence of cardiovascular risk factors and investigate predictors of blood hypertension, dyslipidemia and DM II in PLWH population in order to project a strategy to prevent CVD in PLWH.

Methods

We conducted a single centre retrospective observational cross-sectional study enrolling outpatients with a diagnosis of HIV infection, at least ≥18 years old, followed at the Infectious Diseases and Tropical Medicine Unit of University Hospital "Santa Maria alle Scotte", Siena, with at least one follow-up visit during 2020 and 2021.

Outpatient records were used to collect clinical and laboratory in an anonymized database. The following characteristics were collected: gender at birth, age, ethnicity, smoking attitude, height and weight, time of HIV positivity and time of antiretroviral treatment, use of antiretrovirals, risk factors for acquiring HIV infection, class of infection according to the Centre of Disease Control CDC Atlanta and coinfection with major hepatotropic viruses. Laboratory and clinical values related to HIV infection were collected: CD4 cells count at nadir and last visit, HIV-1 RNA at Zenith and last visit. The optimal immunological recovery (OIR) was defined as CD4 cells count ≥500 cells/μL with CD4 percentage ≥30% and CD4/CD8 ratio ≥1. Lipidic profile during the follow-up was investigated by the absolute value of triglyceride, total cholesterol with high-density lipoprotein (HDL) and low-density lipoprotein (LDL) fractions. Furthermore, we collected the last blood pressure measure, glycaemia, creatinine and estimated glomerular filtration rate (eGFR), which was calculated by CKD-EPI formula (Chronic Kidney Disease Epidemiology Collaboration). Antihypertensive, antidiabetics, lipid-lowering medicaments and current cART were registered at the last follow-up visit. Blood hypertension was defined as a Systolic Blood Pressure ≥140 mmHg and/or Diastolic Blood Pressure ≥90 mmHg or being under antihypertensive medicaments or a defined diagnosis of hypertension. Dyslipidaemia was defined as total cholesterol ≥200 mg/dL and/or LDL ≥160mg/dL or being under lipid-lowering medicaments or a defined diagnosis of dyslipidaemia. DMII was defined by two consecutives fasting blood glucose ≥126 mg/dL or glycohemoglobin (HbA1c) >6,5% or a positive Oral Glucose Tolerance Test (OGTT) or being under antidiabetics or a defined diagnosis of diabetes mellitus type 2. Additionally, we checked a positive anamnesis for major cardiovascular events (CVE), defined as acute myocardial infarction and stroke, and minor, defined as peripheral arterial disease, including haemodynamically relevant supra-aortic plaques, angina pectoris, heart failure, Transient Ischemic Attack, Deep Vein Thrombosis, Acute Pulmonary Embolism, arterial and/or coronary revascularization procedures.

Descriptive analysis and logistic regression analysis were performed to explore factors associated with a cardiovascular risk factor condition, defined

as hypertension, diabetes mellitus type II and dyslipidemia. In univariate analysis we investigate know predictors from the literature for cardiovascular risk factor conditions, variables with a *p value p <0,05* ("two tailed") was considered statistically significant and furthermore investigated in multivariate logistic regression (adjusted odds ratio, aOR, and corresponding 95% confidence interval, CI), correlations with a *p value p <0,05* ("two tailed") was considered statistically significant. The analysis was performed using software SPSS version 24.0 (SPSS Inc., Chicago, IL).

Results

Two-hundreds and eighty-six PLWH were included: the majority males, caucasian, experienced in cART treatment, with median age at the last follow-up of 54.36 years (IQR 46.80-59.54) and 190 (66.4%) were at least 50 years old. The risk factors for acquiring HIV infection were most sexual transmission in 30.7% (heterosexuals 17.1% and Male who have Sex with Males, (MSM), 13.6%). The median Body Mass Index (BMI) was 25 kg/m^2 (IQR 22.49-28.06). One third were smokers and 14.3% former smokers. The median years from the first HIV positive test was 14.67 (IQR 8.08-24.09); 21.7% in CDC class C. The median age at diagnosis was 35.02 years (IQR 28.02-43.78), the median viraemia zenith 44084 copies/mL (n=270 IQR 2340.75-199700) and the median CD4 cells count at nadir 262 cells/µL (n=285 IQR107-411). At the last follow-up the 22.4% had viraemia greater than 20 copies/mL with a median viral load in viraemic patients of 43.5 cp/mL (n=64 IQR 27-129.75). The median CD4 absolute count at the last follow-up was 666 cells/µL (n=285 IQR 464.25-900.5).

The median duration of cART in years was 12.27 (IQR 7.23-19.61), with almost one third had experienced treatment with abacavir, more than half with Protease Inhibitors (PIs), and almost all with nucleos(t)ide reverse transcriptase inhibitor (NRTI). The most used cART was two NRTI and one integrase inhibitor (INSTI) followed by two NRTIs and one non-nucleoside reverse transcriptase inhibitor (NNRTI) and an INSTI with an NRTI in dual regimen. The combinations of ART most used at the time of the last follow-up were BIC/TAF/FTC (28.7%), RPV/TAF/FTC (16.8%), DTG/3TC (10.1%), DRVc/TAF/FTC (7.3%), DTG/ABC/3TC (7%), DTG/RPV (3.5%). Detailed clinical and viro-immunological data are shown in **Table 1**.

Table 1. Clinical and viro-immunological characteristics.

CLINICAL AND VIRO-IMMUNOLOGICAL PARAMETERS (N=286)	
Median years from HIV diagnosis	14.67 (IQR[6] 8.08-24.09, MIN 1-MAX 38)
Naïve	10 (3.50%)
Median age at diagnosis of HIV positivity • >50 yo at diagnosis	35.02 (IQR 28.02-43.78, MIN 1-MAX 71) • 36 (12.60%)
Virological parameters	
• Median VL[1] zenith, cp/mL (N=270)	44084 (IQR 2340.75-199700, MIN 20-MAX 1000000)
Viral Load at last follow-up	• 163 (57%)
• VL negative or undetectable	• 59 (20.60%)
• VL detectable, but <20cp/mL	• 64 (22.40%)
• VL detectable ≥20cp/mL ◦ Median VL cp/mL in VL ≥20cp/mL subgroup (N=64)	43.50 (IQR 27-129.75, MIN 20-MAX 427000)
Immunological parameters	
• OIR[5] at last follow-up	206 (72%)
• Median nadir CD4, *cell/ µL* (N=285)	262 (IQR 107-411, MIN 1-MAX 1188)
◦ <200 *cell/ µL*	• 109 (38.20%)
◦ 200-499 *cell/ µL*	• 135 (47.40%)
◦ > 500 *cell/ µL*	• 41 (14.40%)
• Mediana CD4 at last follow-up, *cell/ µL* (N=285)	666 (IQR 464.25-900.50, MIN 23-MAX 1850)
HBsAg[3] positives	8 (2.80%)
HCV[4] positives	48 (16.80%)
HCV viraemic	1 (0.30%)
• Viral Load HCV (N=1) cp/mL	• 3210
Years in antiretroviral therapy	12.27 (IQR 7.23-19.61, MIN 1-MAX 37)
• <5 years	• 30 (10.50%)
• 5-10 years	• 85 (29.70%)
• 11-15 years	• 66 (23.10%)
• 16-20 years	• 39 (13.60%)
• >20 years	• 66 (23.10%)
Experienced with Abacavir	90 (31.30%)
• Median exposure years	3.5 (IQR 2-6, MIN 1-MAX 20)
Experienced with Protease Inhibitors	181 (62.90%)
• Median exposure *years*	8 (IQR 4-12, MIN 1-MAX 29)
Experienced with NRTI[2]	283 (99%)
Median exposure *years*	11 (IQR 7-18, MIN 1-MAX 37)
Antiretroviral therapy used at the last follow-up (N=284)	
2NRTI[2]+ INSTI[7]	124 (43.70%)
2NRTI+NNRTI[8]	52 (18.30%)
NRTI+INSTI	31 (10.90%)
2NRTI+ PIs[9]	25 (8.80%)
NNRTI+INSTI	12 (4.20%)
INSTI+PIs	10 (3.50%)
NNRTI+-PIs	8 (2.80%)
NRTI+PIs	6 (2.10%)
Others	16 (5.60%)
Last Switch reason in Experienced PLWH (N=274)	
Simplification	122 (44.53%)
Proactive Switch	68 (24.82%)
Toxicity	22 (8.03%)
Intensification	22 (8.03%)
Viral Failure [10]	17 (6.20%)
Drug-drug Interaction	9 (3.28%)
Pregnancy	3 (1.09%)
Immunological Failure	1 (0.36%)
Others	10 (3.65%)

[1] Viral Load; [2] Nucleoside/Nucleotide Reverse Transcriptase Inhibitors ;[3] Hepatitis B Virus Antigen; [4] Hepatitis C Virus; [5] Optimal Immunological Recovery (CD4 counts ≥ 500 cells/ µL, CD4 percentage ≥30%, CD4/CD8 ≥ 1); [6] Interquartile Range; [7] Integrase Strand Transfer Inhibitor, [8] Non-Nucleoside Reverse Transcriptase Inhibitor; [9] Protease Inhibitor; [10] two Viral Load ≥ 50 cp/mL or one ≥ 1000/mL or one ≥ 50 cp/mL after switch

LIPID METABOLISM, PRESSURE AND GLYCAEMIC PARAMETERS AT LAST FOLLOW-UP	
TOTAL CHOLESTEROL (median, mg/dL) (N=284)	190 (IQR[3] 167-218.75 MIN 95- MAX 322)
LDL[1] CHOLESTEROL (median, mg/dL) (N=217)	112 (IQR 91-138 MIN 35-MAX 255)
HDL[2] CHOLESTEROL (median, mg/dL) (N=218)	48 (IQR 41-60 MIN 25-MAX 117)
TRIGLYCERIDES (median, mg/dL) (N=280)	118 (IQR 81-164.5 MIN 37-MAX 525)
DYSLIPIDEMIA DIAGNOSIS (N=286)[4]	162 (56.6%)
USE OF ORAL LIPID-LOWERING AGENTS IN DYSLIPIDEMICS (N=162)	
• Diet and lifestyle	87 (53.70%)
• Statins	16 (9.90%)
• Ezetimibe	6 (3,70%)
• Statins+ Ezetimibe	4 (2.50%)
• Fibrate	9 (5.60%)
• Phytosterol	6 (3.70%)
• Omega3	13 (8.00%)
• Statins/omega3	4 (2.50%)
• Ezetimibe/fibrate	2 (1.20%)
• Ezetimibe/omega3	2 (1.20%)
• Statins/ezetimibe/omega3	2(1.20%)
• Fibrate/omega3	6 (3.70%)
• PSCK9[5] inhibitors /omega3	2(1.20%)
• Phytosterol/omega3	1 (0.60%)
• Fibrate/statins/omega3	1 (0.60%)
• Fibrate/omega3/phytosterol	
SYSTOLIC BLOOD PRESSURE (median, mmHg) (N=240)	120 (IQR[3] 110-130 MIN 90-MAX 170)
DIASTOLIC BLOOD PRESSURE (median, mmHg) (N=240)	75 (IQR 70-80 MIN 58-MAX 100)
BLOOD HYPERTENSION[6] (median, mmHg) (N=286)	108 (37.80%)
USE OF ANTIHYPERTENSIVES AGENTS IN HYPERTENSIVE PATIENTS (N=108)	
• Diet and lifestyle	24 (22.20%)
• Monotherapy	39 (36.10%)
• Dual Therapy	32 (29.70%)
• Triple Therapy	12 (11.10%)
• Quadruple Therapy	1 (0.90%)
GLYCAEMIA (median, *mg/dL*) (N=284)	93 (IQR[3] 85.25-101 MIN 65-MAX 264)
DIAGNOSIS OF DIABETES[7] (N=286)	20 (7%)
USE OF HYPOGLYCEMIC AGENTS IN DIABETICS (N=20)	
• Diet and lifestyle	6 (30%)
• Insulin	10 (50%)
• Metformin	3 (15%)
• GLP1[8] Agonist	1 (5%)

[1] Low Density Lipoprotein;[2] Hight Density Lipoprotein; [3] Interquartile Range; [4] LDL 160 mg/dL or lipid-lowering agents use or total Cholesterol 200 mg/dL or previous dyslipidemia diagnosis;[5] Proprotein of Convertase Subtilisin/Kexin type 9; [6] Systolic Blood Pressure ≥ 140mmHg or Diastolic Blood Pressure ≥ 90mmHg or use of antihypertensives agents or previous Hypertension diagnosis, [7] two fast glycaemia ≥ 126 mg/dL o glycated Haemoglobin ≥ 6.5% or glycaemia ≥ 200mg/dL after oral load of 75g glucose and symptoms or previous diabetes diagnosis; [8] Glucagon-like peptide 1

Table 2. Lipidic metabolism, blood pressure, and glycaemic parameters.

Dyslipidaemia was found in 162 individuals (56.6%) and 46,3% of these was used at least one lipid-lowering drug. Overall, 108 individuals (37.8%) had a diagnosis of arterial hypertension; of these, the majority were under antihypertensive therapy, most of them in combination therapy and only the 36.1% on monotherapy, the 22.2% were on treatment with dietary and lifestyle changes without any drugs. Twenty individuals (7%) had a diagnosis of DM II; 10 on insulin therapy. Median creatinine was 0.96 mg/dL (IQR 0.85-1.08) and the median estimated GFR was 84.7 mL/min/1.73 m2. According to GFR (stratified according to the guidelines of the American National Kidney Foundation) 38.5% had a normal renal function with a GFR of at least 90 mL/min/1.73 m^2. Nine subjects presented at least one major CVE, 7 an acute myocardial infarction (AMI) and 2 a stroke, with a median age from first detection of HIV infection of 16.12 years (IQR 8.93-26.83). In two cases there was a second major cardiovascular event (AMI) with a median time from HIV diagnosis of 18.94 years (IQR 15.01-18.94). Overall, 27 subjects experienced at least one minor CVE after a median of 14.66 years from HIV diagnosis (IQR 8.93-26.86). In 4 cases a second minor cardiovascular event followed, at a median distance from HIV diagnosis of 12.12 years (IQR 8.11-24.45) and in one case a third event after HIV diagnosis of 28 years. Details concerning lipid metabolism, blood pressure and glycemia are shown in **Table 2**.

Variables associated with Cardio vascular risk factors.

In multivariate logistic analysis, factors associated with dyslipidemia in PLWH were blood hypertension (aOR 2.21 95%CI 1.25-3.88, *p 0.006*), exposure to protease inhibitors (aOR 2.08, 95%CI 1.21-3.58, *p 0.008*), age greater than 50 years (aOR 1.93, 95%CI 1.10-3.39, *p 0.021*) and detectable viremia (aOR 1.90, 95%CI 1.11-3.26, *p 0.019*). There was an inverse correlation between HCV positivity and dyslipidemia (aOR 0.29, 95%CI 0.14-0.61 *p<0.001*) (**Figure 1**).

In multivariate logistic analysis, variables associated with blood hypertension were dyslipidemia (aOR 2.87, 95%CI 1.52-5.44, *p 0.001*), age greater than 50 years (aOR 2.62, 95%CI 1.31-5.23, *p 0.006*) and a BMI greater than 30 kg/m^2 (aOR of 5.18, 95%CI 2.17-13.38, *p<0.001*) (**Figure 2**).

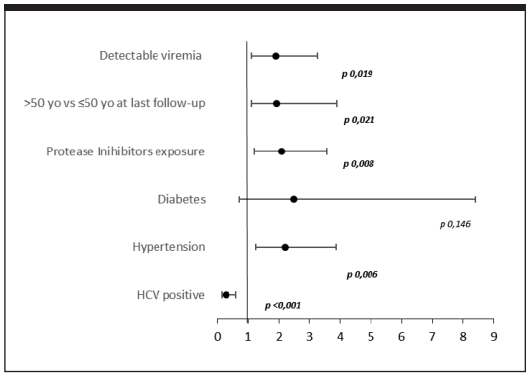

Figure 1. Variables associated with dyslipidemia.

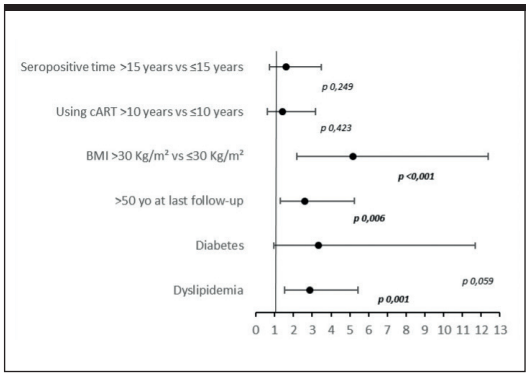

Figure 2. Variables associated with blood hypertension.

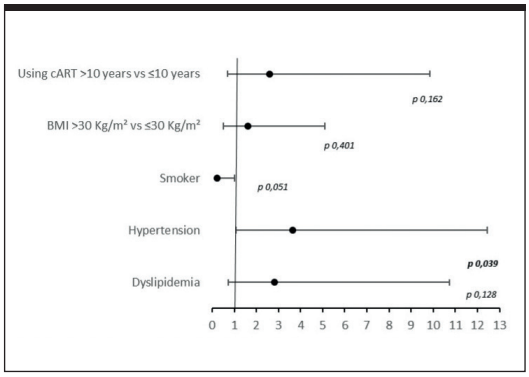

Figure 3. Variables associated with Diabetes Mellitus type 2.

In multivariate logistic analysis, arterial hypertension was associated with diabetes mellitus (aOR 3.65, 95%CI 1.07-12.44, *p 0.039*) (**Figure 3**).

Discussion

Currently in Western countries cardiovascular diseases are the leading cause of morbidity and mortality in PLWH, as in the general population, both due to aging and factors HIV specific, such as chronic inflammation and antiretroviral therapies (2).

Our study showed that the median age of the PLWH was 54.36 years, in agreement with recent studies which estimate that at least 50% of currently PLWH individuals in Western countries have an age greater than 50 years and non-infectious comorbidities in PLWHs are more precocious and more prevalent than in the general population (1).

Overall, the proportion of smokers is higher than the Italian median, 37.8% compared to 18.4% (15), suggesting how to quit smoking is essential in this setting (6).

As expected, due to the addition of traditional risk factors, such as age greater than 50 years, and those specific for PLWH, as prior PIs use and the presence of detectable viraemia, dyslipidemia is the most frequent CVRF (8).

Aging is a well-known risk factor related to alterations of the lipid profile through changes in the endothelium of the hepatic sinusoids, alterations in postprandial lipaemia, hormones and the activity of specific receptors (16). The association between hypertension and dyslipidemia is not only a cumulative risk but is reciprocal and synergistic in implementing cardiovascular risk, for underlying this concept was proposed in literature the term *"Lipitension",* in particular, hypertension is a risk factor for the development of dyslipidemia acting with a kidney and liver damage with subversion of endothelial and consequent alteration of renin-angiotensin-aldosterone and other hormones patterns (17). DMII is confirmed as a risk factor for the close interconnection between glucose and lipid metabolism, with qualitative and quantitative changes of lipoproteins in diabetic patients as known from the literature (18). The use of PIs, in particular first generation or boosting ritonavir (19), increases triglycerides and LDL both in PLWH and negative controls (20). Detectable viremia is also a risk factor for developing lipid profile alterations, confirming the role of chronic inflammation and the persistence of HIV in altering lipid metabolism, as suggested in the literature (21).

It is clear the need for lifestyle intervention, early screening of lipid alterations and the use, where necessary, of lipid-lowering drugs and switch to

less lipidic-impacting cART as suggested by recent Italian reviews (8).
In our study population, blood hypertension represented the second most prevalent risk factor, slightly higher than the Italian general population, 37.8% vs 31% (22) but in agreement with data from other cohorts of PLWH (23).
The age over 50 years, dyslipidemia and a BMI >30 kg/m^2 resulted as risk factors for the development of hypertension according to the literature (24). We found an inverse correlation between dyslipidaemia and HCV infection because we defined dyslipidemia as total cholesterol ≥200 mg/dL and/or LDL ≥160mg/dL; as known from literature, in people infected with HCV LDL-cholesterol is reduced because of the alteration of liver lipids metabolism, this reduction of LDL is not a protective against cardiovascular events and ,as well documented in literature, in HCV positive individuals the cardiovascular risk is greater than the general population (25). Managing blood hypertension looks fundamental; studies conducted on PLWH show that hypertension is associated with a higher risk of CVD, particularly for the development of AMI and strokes as underlined by meta-analysis (26) and several data from large cohorts (27; 28).
In agreement with other PLWH cohort findings, 7% of the enrolled were affected by diabetes mellitus (29). Blood hypertension emerged as a risk factor for DMII, confirming the role of hypertension in the development of diabetes mellitus as known in cohorts of PLWH (29) and non-infected people (30).

Limits and possible bias of the study

It should be emphasized that possible limits of our analysis are the low number of PLWH enrolled, the retrospective nature of the study and the monocentric origin of data. In particular we need studies that include more PLWH to investigate better the predictors for cardiovascular risk conditions, especially for the development of DMII due to the limited number of diabetics PLWH enrolled in our study.
Furthermore, even if dyslipidemia, DM II and blood hypertension are mutually and strictly interconnected, a possible bias of our analysis is the risk of reverse casualty between these cardiovascular risk conditions. Moreover, we analyse the exposure to different classes of cART but not all, at the time of the study the role of integrase inhibitors on BMI and consequent cardiovascular risk was not investigated, furthermore studies in this field are required. It's clear that the field of investigation is open and needs more research, preferably with multicentric and perspective studies.

Conclusion

Due to the effectiveness of cART and the higher age at diagnosis of HIV, in not-limited-resource-countries the age of PLWH is increasing. However, new infections are decreasing, and they are no longer exposed to the burden of AIDS-related diseases in terms of mortality and morbidity.
The burden of Cardiovascular Diseases has increased due to aging, the direct effect of chronic immune activation carried by the persistence of virus infection side effects of therapy, habits and lifestyle. In this setting, the prevalence of Cardiovascular Risk Factors and the incidence of cardiovascular diseases is higher and earlier than in the general population. Furthermore, peculiar risk factor has a strong effect other than general risk predictors. Although further investigations are needed to better understand the risk factors for the development of Cardiovascular Risk Factors and Cardiovascular Diseases, it is helpful to provide early focused screening, using risk assessment scales explicitly designed for PLWH integrating them with the classic assessment scales.
Moreover, it is mandatory to promote a healthy lifestyle and to treat hypertension and dyslipidemia pharmacologically, if necessary, paying attention to interactions with cART.
The global interventions to reduce and prevent Cardiovascular Risk Factors will be useful to improve the quality and expectancy of life in PLWH by reducing the multi-pathology burden and improving health indicators.

Other information:

A special memory by the authors should be reserved for the mourning Dr. Mauro Ruggeri, General Practitioner and tutor of the Specific Training Course on General Practice, Florence, attended by the first author of this study during the enrolling phase, who passed away in 2022. ■

REFERENCES

1. Guaraldi G, Milic J, Mussini C. *Aging with HIV. Curr HIV/AIDS Rep.* 2019 Dec;16(6):475-481.

2. Shahbaz S, Manicardi M, Guaraldi G, Raggi P. *Cardiovascular disease in human immunodeficiency virus infected patients: A true or perceived risk?* World J Cardiol. 2015 Oct 26;7(10):633-44.

3. So-Armah K, Benjamin LA, Bloomfield GS, et al. *HIV and cardiovascular disease. Lancet HIV.* 2020 Apr;7(4):e279-e293.

4. Siedner MJ. *START or SMART? Timing of Antiretroviral Therapy Initiation and Cardiovascular Risk for People With Human Immunodeficiency Virus Infection. Open Forum Infect Dis.* 2016 Feb 9;3(1):ofw032.

5. Silverberg MJ, Leyden WA, Xu L, et al. *Immunodeficiency and risk of myocardial infarction among HIV-positive individuals with access to care. J Acquir Immune Defic Syndr.* 2014 Feb 1;65(2):160-6.

6. De Socio GV, Pasqualini M, Ricci E, et al. *Smoking habits in HIV-infected people compared with the general population in Italy: a cross-sectional study. BMC Public Health.* 2020 May 20;20(1):734.

7. Siddiqui M, Hannon L, Wang Z, et al. *Hypertension and Cardiovascular Disease Risk Among Individuals With Versus Without HIV.* Hypertension. 2023 Apr;80(4):852-860.

8. Maggi P, Di Biagio A, Rusconi S, et al. *Cardiovascular risk and dyslipidemia among persons living with HIV: a review.* BMC Infect Dis. 2017 Aug 9;17(1):551.

9. Sarkar S, Brown TT. *Diabetes in People with HIV.* Curr Diab Rep. 2021 Mar 17;21(5):13.

10. Achhra AC, Lyass A, Borowsky L, et al. *Assessing Cardiovascular Risk in People Living with HIV: Current Tools and Limitations.* Curr HIV/AIDS Rep. 2021 Aug;18(4):271-279.

11. Delabays B, Cavassini M, Damas J, et al. *Cardiovascular risk assessment in people living with HIV compared to the general population.* Eur J Prev Cardiol. 2022 Mar 30;29(4):689-699.

12. M Smit, R Cassidy, A Cozzi-Lepri, et al. *Projections of non-communicable disease and health care costs among HIV-positive persons in Italy and the U.S.A.: A modelling study. PLoS One.* 2017 Oct 23;12(10):e0186638.

13. Douglas PS, Umbleja T, Bloomfield GS,et al. *Cardiovascular Risk and Health Among People With Human Immunodeficiency Virus (HIV) Eligible for Primary Prevention: Insights From the REPRIEVE Trial.* Clin Infect Dis. 2021 Dec 6;73(11):2009-2022.

14. Maggi P, De Socio GV, Cicalini S, et al. *Statins and aspirin in the prevention of cardiovascular disease among HIV-positive patients between controversies and unmet needs: review of the literature and suggestions for a friendly use.* AIDS Res Ther. 2019 May 24;16(1):11.

15. *Ministero della Salute Direzione generale della comunicazione e dei rapporti europei e internazionali Ufficio 2 Direzione generale della prevenzione sanitaria Ufficio 8. Prevenzione e controllo del tabagismo.* A cura di Ministero della Salute. Maggio 2020. [Online] https://www.salute.gov.it/imgs/C_17_pubblicazioni_2916_allegato.pdf (last visit 15/08/2023)

16. Liu HH, Li JJ. *Aging and dyslipidemia: a review of potential mechanisms.* Ageing Res Rev. 2015 Jan;19:43-52.

17. Dalal JJ, Padmanabhan TN, Jain P, Patil S, Vasnawala H, Gulati A. *LIPITENSION: Interplay between dyslipidemia and hypertension.* Indian J Endocrinol Metab. 2012 Mar;16(2):240-5.

18. Parhofer KG. *Interaction between Glucose and Lipid Metabolism: More than Diabetic Dyslipidemia.* Diabetes Metab J. 2015 Oct;39(5):353-62.

19. Alvi RM, Neilan AM, Tariq N, et al. *Protease Inhibitors and Cardiovascular Outcomes in Patients With HIV and Heart Failure.* J Am Coll Cardiol. 2018 Jul 31;72(5):518-530.

20. Feeney ER, Mallon PW. *HIV and HAART-Associated Dyslipidemia.* Open Cardiovasc Med J. 2011;5:49-63.

21. Bowman E, Funderburg NT. *Lipidome Abnormalities and Cardiovascular Disease Risk in HIV Infection.* Curr HIV/AIDS Rep. 2019 Jun;16(3):214-223.

22. S Giampaoli, MF Vescio, A Gaggioli, D Vannuzzo *Gruppo di Ricerca dell'Osservatorio Epidemiologico Cardiovascolare. Prevalenza dell'ipertensione arteriosa nella popolazione italiana.* EPICENTRO Istituto Superiore di Sanità. [Online] https://www.epicentro.iss.it/ben/2002/settembre02/2 (last visit 15/08/2023)

23. Baekken M, Os I, Sandvik L, Oektedalen O. *Hypertension in an urban HIV-positive population compared with the general population: influence of combination antiretroviral therapy.* J Hypertens. 2008 Nov;26(11):2126-33.

24. Fahme SA, Bloomfield GS, Peck R. *Hypertension in HIV-Infected Adults: Novel Pathophysiologic Mechanisms.* Hypertension. 2018 Jul;72(1):44-55.

25. Elgretli W, Chen T, Kronfli N, Sebastiani G. *Hepatitis C Virus-Lipid Interplay: Pathogenesis and Clinical Impact.* Biomedicines. 2023 Jan 19;11(2):271.

26. Rao SG, Galaviz KI, Gay HC, et al. *Factors Associated With Excess Myocardial Infarction Risk in HIV-Infected Adults: A Systematic Review and Meta-analysis.* J Acquir Immune Defic Syndr. 2019 Jun 1;81(2):224-230.

27. Armah KA, Chang CC, Baker JV, et al. *Prehypertension, hypertension, and the risk of acute myocardial infarction in HIV-infected and -uninfected veterans.* Clin Infect Dis. 2014 Jan;58(1):121-9.

28. Hatleberg CI, Ryom L, Kamara D, et al. *Predictors of Ischemic and Hemorrhagic Strokes Among People Living With HIV: The D:A:D International Prospective Multicohort Study*; EClinicalMedicine, Volume 13, 2019, Pages 91-100, ISSN 2589-5370.

29. da Cunha GH, Franco KB, Galvão MTG, et al. *Diabetes mellitus in people living with HIV/AIDS: prevalence and associated risk factors. AIDS Care.* 2020 May;32(5):600-607.

30. Li X, Wang J, Shen X, et al. *Higher blood pressure predicts diabetes and enhances long-term risk of cardiovascular disease events in individuals with impaired glucose tolerance: Twenty-three-year follow-up of the Daqing diabetes prevention study.* J Diabetes. 2019 Jul;11(7):593-598.