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Cardiovascular disease and prevention among people living with HIV in South Florida

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Abstract

Antiretroviral therapy (ART) has improved survival of patients living with HIV (PLWH); however, this has been accompanied by an increase in cardiovascular disease (CVD). Although preventative measures for CVD among the general population are well described, information is limited about CVD prevention among PLWH. The goal of this study was to characterize the prevalence of CVD in our population and to assess the use of primary and secondary prevention.

We performed a retrospective review of PLWH receiving primary care at a large academic center in Miami, Florida. We characterized the prevalence of CVD, CVD risk, and the use of aspirin and statins for primary and secondary CVD prevention.

A total of 985 charts were reviewed (45% women, 55% men). Average age was 52.2 years. Average CD4 count was 568 cells/microL. 92.9% were receiving ART, and 71% were virologically suppressed. The median 10-year ASCVD risk was 7.3%. The prevalence of CVD was 10.4% (N = 102). The odds of having CVD was lower in patients on ART (OR 0.47, 95% CI: 0.25–0.90, $P = .02$). The use of medications for primary and secondary prevention of CVD based on current guidelines was low: 15% and 37% for aspirin respectively, and 25% and 44% for statins.

CVD risk and rates of CVD are high among PLWH and receiving ART could protect against CVD. However, the use of medications for primary and secondary prevention is low. Increased awareness of CVD risk-reduction strategies is needed among providers of PLWH to decrease the burden of CVD.

Abbreviations: ART = antiretroviral therapy, ASCVD = atherosclerotic cardiovascular disease, CD4 = CD4+ T helper cells, CI = confidence interval, CVD = cardiovascular disease, HbA1c = hemoglobin A1C, HIV = human immunodeficiency virus, IQR = interquartile range, IRB = Institutional Review Board, LDL-C = low-density lipoprotein cholesterol, OR = odds ratio, PLWH = patients living with HIV, SD = standard deviation.

Keywords: cardiovascular disease, epidemiology, HIV, primary prevention, secondary prevention

1. Introduction

The advent and improved accessibility to anti-retroviral therapy (ART) for the treatment of HIV has afforded patients living with HIV (PLWH) an increased life expectancy.[1] Subsequently, these patients are now manifesting the burden of chronic, non-communicable diseases, such as cardiovascular disease (CVD).[2–4] CVD is the leading cause of death in PLWH, with a nearly 2-fold increased incidence of cardiovascular events compared with uninfected counterparts.[5,6] It has been previously shown that PLWH have higher rates of CVD compared with HIV-uninfected controls in all age groups.[7]

Multiple factors have been thought to contribute to the development of CVD among PLWH.[8–10] These include a high prevalence of traditional CVD risk factors, such as smoking, hypertension, obesity, and diabetes mellitus, the presence of chronic inflammation and immune activation associated with aging and HIV, as well as the cardiometabolic dysfunction associated with the use of some ARTs.[2,11–15] In combination, these factors lead to a prothrombotic state, the presence of vascular dysfunction, and the subsequent development of frank CVD.[16–22]

Statin medications, used to decrease lipid abnormalities, possess anti-inflammatory properties that may limit vascular and myocardial inflammation, subsequently reducing atherogenesis.[23,24] There are strong data supporting statin use for both

primary and secondary prevention of cardiovascular disease among the general population.[25–27] Based on current guidelines, the role of statin therapy in primary prevention is determined by the Atherosclerotic Cardiovascular Disease (ASCVD) Risk Score.[26] However, conventional stratification models such as ASCVD and Framingham risk scores have been shown to underestimate risk in PLWH and do not take into account nonconventional risk factors, such as subclinical inflammation and noncalcified plaques, which often affect PLWH.[12,28,29] Yet, current models that incorporate inflammatory markers and ART regimens do not improve model performance and lack external validity.[13,30] As a result, the American College of Cardiology 2018 guidelines for the management of blood cholesterol have aimed to bridge this risk estimation gap by including HIV as "risk enhancing factors" to restratify higher risk groups that may benefit from the use of statins.[31] Still, information is limited regarding the use of these medication for CVD prevention among PLWH.

The state of Florida ranks among states with the highest overall prevalence of HIV in the United States, with Miami-Dade County in particular having the highest annual rate of newly diagnosed cases in 2017, per the Center for Disease Control and Prevention's 2018 report.[32] Further, Jackson Memorial Hospital administers the greatest number of HIV diagnostic assays in Miami, FL, and most of the PLWH in Miami are older than 50 years of age.[33] The Center for Disease Control estimates that nearly 90% of this population with newly diagnosed HIV is composed of Hispanic and non-Hispanic black individuals.[2,34] This study aims to identify the prevalence of CVD, CVD risk, and the use of aspirin and statins for primary and secondary CVD prevention among PLWH who receive HIV care at a large academic center in Miami, Florida.

2. Methods

This study was reviewed and approved by the Institutional Review Board at the University of Miami (IRB Number 20161109). This was a retrospective chart review of patients seen between 2017 and 2019 at the Jackson Memorial Hospital Special Immunology Clinic, located on the University of Miami/Jackson Memorial Hospital medical campus. This clinic serves as the HIV subspecialty care clinic and provides primary care for PLWH. The majority of the patients are from underrepresented minorities, older than 50 years of age, have low income, and receive HIV care through the Ryan White Program. No patients under the age of 18 were included in this study. The electronic medical record was used as the source of information. This entailed reviewing clinic notes, anthropometric data, laboratory tests, and diagnostic tests.

Physician notes were reviewed to identify the diagnoses of previous cardiovascular disease, relevant comorbidities (such as diabetes, chronic kidney disease, etc.), prescription of CVD and HIV-related medications, and lifestyle behaviors such as smoking or drug use. Anthropometric data were reviewed for blood pressure and body mass index. Review of laboratory tests included HIV-related markers such as CD4 counts and viral loads, and markers for cardiovascular risk such as cholesterol panels and hemoglobin A1C. We reviewed diagnostic testing for cardiovascular diseases that were on file, including echocardiograms and cardiac catheterization.

CVD was defined as the presence of any of the following: coronary artery disease, myocardial infarction, angina, periph-eral artery disease, cerebrovascular disease, congestive heart failure, or atrial fibrillation/atrial flutter. We considered essential hypertension, defined as the use of antihypertensives, as a risk factor for the development of CVD, but did not include it in our CVD prevalence estimates.

All data reviewed from the electronic medical record were deidentified and populated in a secure, encrypted online database using the RedCap electronic data capture tool.[35] Statistical analyses were performed on reports generated from RedCap using Stata.[36]

Individuals with a diagnosed history of CVD were identified and prevalence was estimated for this population. ASCVD scores were calculated for all patients ages 40 to 79 for whom the necessary data was available (systolic blood pressure, lipid panel, smoking history, etc.). The prescription of antiplatelet and cholesterol-lowering medications for primary prevention in patients without known CVD was evaluated. This analysis was based on the latest guidelines from the United States Preventative Service Task Force.[26] Among patients ages 50 to 70 with an ASCVD greater than 10%, we analyzed the number of individuals who were prescribed aspirin for primary prevention. In addition, we analyzed the number of individuals who were prescribed a statin for primary prevention among patients ages 40 to 75 with an ASCVD greater than 7.5%.[26] We also analyzed the proportion of diabetic patients on a statin, as well as the proportion of patients with hyperlipidemia on a statin. We analyzed the uptake of antiplatelet and cholesterol-lowering medications for secondary prevention in patients with a diagnosed history of CVD.

To identify statistically significant differences in demographic and laboratory variables between PLWH with CVD and those without CVD, we used either t tests or Mann–Whitney U tests. For differences in categorical variables, we used Pearson Chi-Squared tests. P values less than .05 were considered significant. Univariate linear models were used to evaluate the relationship between ASCVD scores and HIV-related factors such as CD4 count and viral load. Multivariate logistic models with documented CVD as the binary outcome were used to identify possible predictors of CVD. We added variables in a step-wise fashion based on clinical judgement and known and hypothesized relationships between HIV and CVD.

3. Results

A total of 985 charts of PLWH were reviewed. Patients' median age was 53 years old (Fig. 1), with a large percentage of women and a demographically diverse population (Table 1). The total prevalence of cardiovascular disease in this cohort was 10.4% (n = 102), 11.0% prevalence in males, and 9.6% in females. A total of 141 cardiovascular events were identified, with the subtypes of CVD described in Table 2. Some patients had more than one cardiovascular event, hence the difference between prevalence and total events. In patients 40 to 79 years of age, the median 10-year ASCVD score for our population was 7.3% (IQR 2.9–14.4), and the average ASCVD score was 10.7% (SD 10.9). The distribution was heavily skewed to the left as shown in Figure 2.

We compared clinically relevant characteristics between seropositive individuals with a history of CVD (n = 102) to those without a history of CVD (n = 883). PLWH with CVD were significantly older than PLWH without CVD (59.8 vs 51.3 years, $P < .001$), with similar gender composition between groups.
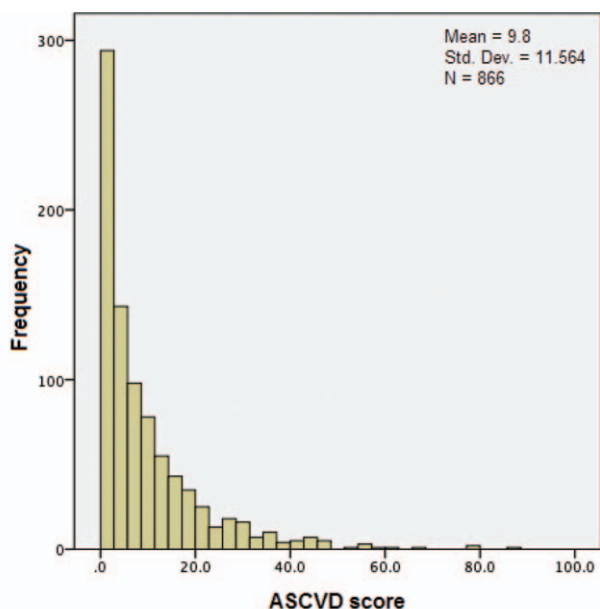
ASCVD: Atherosclerotic cardiovascular disease

Figure 1. *Age distribution of cohort.* Histogram displaying the age distribution of patients that were analyzed as part of the study (n=985).

PLWH with CVD had a lower proportion of Hispanic ethnicity but higher proportion of African American race ($P=.003$). Diagnosis of hypertension ($P<.001$), chronic kidney disease ($P<.001$), diabetes ($P<.001$), and hyperlipidemia ($P=.004$) were all significantly more frequent in patients with CVD. There was no difference in history of tobacco use, median blood pressures, and body-mass indices; however, PLWH with CVD

had a lower median low-density lipoprotein cholesterol (LDL-C) and higher median HbA1c.

Aspirin was prescribed in 11% of the entire cohort (n=107/985). The use of aspirin for primary prevention in patients ages 50 to 70 with an ASCVD risk score ≥ 10% was 15% (n=40/262). The use of aspirin for secondary prevention in patients was 37% (n=38/102). Statins were prescribed in 26% of the entire cohort (n=253/985). The use of statins for primary prevention in patients ages 40 to 75 with an ASCVD risk score ≥ 7.5% was 25% (n=70/276). The use of statins for secondary prevention in patients was 44% (n=45/102). Statins were prescribed for 58% of diabetic patients (n=97/166) (Supplemental Table 3, http://links.lww.com/MD/G247).

On review of HIV-related factors, the average CD4 count was 568.1 ± 337 cells/mm^3, with median viral load of <20 IU/mL (IQR 0–31). Notably, 71.2% of cohort patients had an undetectable viral load (<20 IU/mL), and 92.9% of patients were on ART. However, PLWH with CVD had significantly lower proportion of ART treatment (87.3% vs 93.5%, $P=.019$) despite no statistically significant difference in viral load or most recent CD4 count.

We used logistic regression with history of cardiovascular disease as the outcome to identify predictors of CVD. In a univariate model, being on ART was found to be protective against CVD (OR 0.47, 95% CI [0.25–0.90], $P=.022$, Table 2). This effect remained statistically significant after controlling for age, sex, diabetes, and smoking history (OR 0.37, 95% CI [0.19–0.74], $P=.005$, Supplemental Table 2, http://links.lww.com/MD/G247). An undetectable viral load was associated with 23.7% lower odds of having CVD, but this was not statistically significant (OR 0.763, 95% CI [0.49–1.18], $P=.23$, Table 2).

In multivariate logistic models (Supplemental Table 2, http://links.lww.com/MD/G247), age remained a consistently significant predictor in all models, with a 7.0% higher odds of having

Table 1

Characteristics of PLWH with and without history of CVD.

	Overall (n=985)	History of CVD (n=102)	Without CVD (n=883)	P value
Sociodemographic factors				
Average age (years)	52.2 (SD 11.7) (range 22–88)	59.8	51.3	<.001
Gender	45% Female (447) 55% Male (538)	42% Female (43) 58% Male (59)	46% Female (406) 54% Male (477)	.490
Race/ethnicity	62% Black or AA (614) 33% Hispanic (329) 4% White (37) 1% Others (5)	72% Black or AA (73) 21% Hispanic (21) 7% White (7) 1% Others (1)	61% Black or AA (541) 35% Hispanic (308) 3% White (30) 1% Others (4)	.003
CVD factors				
Smoking history	Yes: 24% (235) No: 76% (750)	Yes: 25% (25) No: 75% (77)	Yes: 24% (210) No: 76% (673)	.871
Diagnosis of hypertension	Yes: 43% (428) No: 57% (557)	Yes: 75% (76) No: 25% (26)	Yes: 40% (352) No: 60% (531)	<.001
Diagnosis of chronic kidney disease	Yes: 11% (111) No: 89% (874)	Yes: 28% (29) No: 72% (73)	Yes: 9% (82) No: 91% (801)	<.001
Diagnosis of diabetes	Yes: 17% (166) No: 83% (819)	Yes: 30% (31) No: 70% (71)	Yes: 15% (135) No: 85% (748)	<.001
Diagnosis of obesity	Yes: 35% (341) No: 65% (625)	Yes: 35% (36) No: 65% (66)	Yes: 35% (305) No: 65% (559)	.999
Diagnosis of Hyperlipidemia	Yes: 43% (378) No: 57% (499)	Yes: 57% (52) No: 43% (39)	Yes: 41% (326) No: 59% (463)	.004
Median BMI (kg/m^3)	27.9 (IQR 23.9–32.1)	27.3 (IQR 23.9–32.7)	28.0 (IQR 24.0–32.1)	.804
Median A1C (%)	5.6 (IQR 5.3–6.0)	5.8 (IQR 5.4–7.1)	5.6 (IQR 5.3–5.9)	.003
HIV factors				
Median CD4 Count (cells/mm^3)	531 (IQR 326– 794)	482 (IQR 272–738)	536 (IQR 331–799)	.148
Median viral load (copies/mL)	0 (IQR 0–31, x̄=8263)	0 (IQR 0–58, x̄=15,081)	0 (IQR 0–29, x̄=7490)	.216
Receiving ART	Yes: 93% (915) No: 7% (70)	Yes: 87% (89) No: 13% (13)	Yes: 94% (826) No: 6% (57)	.019
Undetectable viral load	Yes: 71% (682) No: 29% (276)	Yes: 66% (66) No: 34% (34)	Yes: 72% (616) No: 28% (242)	.226

Table displaying the characteristics of the patients who were part of the chart review, categorized by sociodemographics, known cardiovascular disease factors, and HIV factors. The table also compares the characteristics of patients with documented CVD to those without documented CVD, with either *t* test or Mann–Whitney *U* test. For differences in categorical variables, Pearson Chi-Squared test was used.
A1C = glycated hemoglobin, AA = African American, ART = antiretroviral therapy, BMI = body mass index, CVD = cardiovascular disease, HIV = human immunodeficiency virus, IQR = interquartile range, PLWH = people living with HIV, SD = standard deviation, x̄ = mean.

Table 2

Prevalence and CVD diagnosis among PLWH; and odds of CVD by HIV factors.

	Number of patients	n	%
Total prevalence of CVD	102	985	10.4%
Prevalence of CVD in Males	59	538	11.0%
Prevalence of CVD in Females	43	447	9.6%

	Number of events	n	%
Total CVD events	141		
Coronary artery disease	17	985	1.7%
Myocardial infarctions	19	985	1.9%
Angina	16	985	1.6%
Peripheral vascular disease	23	985	2.3%
Cerebrovascular disease	24	985	2.4%
Congestive heart failure	27	985	2.7%
Atrial fibrillation/flutter	15	985	1.5%

	Odds ratio	95% CI	P value
Odds of CVD by undetectable status (log regression)	0.76	0.49–1.18	.23
Odds of CVD by ART status (log regression)	0.47	0.25–0.90	.022

Table displaying the number of cardiovascular disease events identified among patients with HIV, categorized by type of event. The table also reports the odds of cardiovascular disease by undetectable HIV status as well as the odds of cardiovascular disease by treatment with antiretroviral therapy. ART = antiretroviral therapy, CVD = cardiovascular disease, HIV = human immunodeficiency virus, PLWH = people living with HIV.

CVD for every year of life (OR 1.07, $P < .001$), even after controlling for viral suppression and other demographic and lifestyle variables. Gender was not a significant predictor in our models. However, being diabetic was associated with an
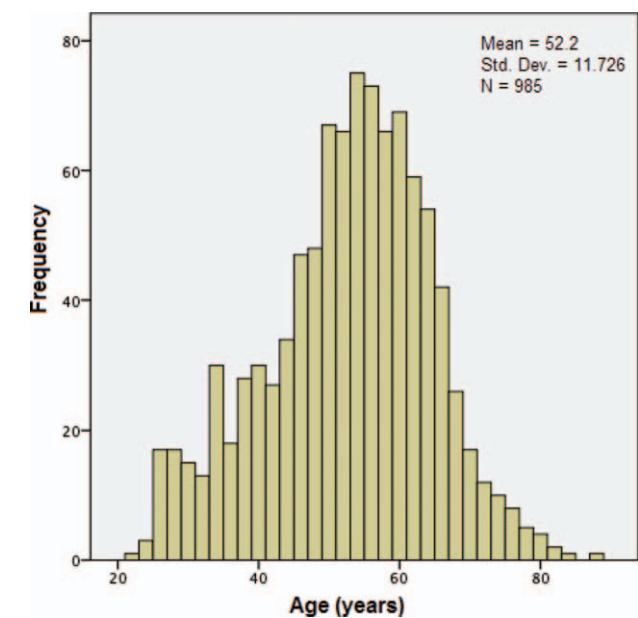
Figure 2. *Distribution of ASCVD scores.* Histogram displaying the distribution of ASCVD scores of patients for whom ASCVD scores could be calculated (n = 866).

approximately 1.7-fold higher odds of having CVD (OR 1.74, $P = .03$). CD4 count was shown to have a minimal protective effect against CVD after controlling for demographic and lifestyle variables, with a 0.1% lower odds for each CD4 cell, but it was not statistically significant (OR 0.999, $P = .107$, Supplemental Table 2, http://links.lww.com/MD/G247).

In evaluating predictors of ASCVD risk, neither CD4 count ($P = .57$) nor viral loads ($P = .28$) were significantly correlated with ASCVD 10-year estimated risk score in eligible patients (Supplemental Table 1, http://links.lww.com/MD/G247). Univariate linear models with ASCVD score as a continuous variable did not reveal a significant association with CD4 counts or viral loads (Supplemental Table 1, http://links.lww.com/MD/G247). Median ASCVD scores did not significantly differ between undetectable viral load (7.4% for undetectable vs 6.7% for detectable, $P = .39$) or ART status (9.7% on ART vs 7.2% not on ART, $P = .10$, Supplemental Table 1, http://links.lww.com/MD/G247).

4. Discussion

This study was the first to characterize the prevalence of CVD, CVD risk, and the use of aspirin and statins for primary and secondary CVD prevention among PLWH who receive HIV care in South Florida.

Results highlight that the overall prevalence of CVD amongst PLWH is high. These results are consistent with the AGE-IV Cohort Study in Amsterdam, which found a CVD prevalence of 10% among seropositive patients.[37] However the prevalence of myocardial infarction (1.9%) and cerebrovascular disease (2.4%) was found to be higher than previous reports (0.42% and 0.6% respectively) among PLWH.[38,39] This is of concern as, PLWH with a history of myocardial infarction, cardiomyopathy, heart failure, or arrhythmia, have been shown to have a 4.5-fold increased risk for sudden cardiac death.[40] Only 2.3% of our cohort carried a diagnosis of peripheral arterial disease, which is lower than other cohort studies, which report a peripheral artery disease prevalence between 4.4% and 12.3% among PLWH.[41,42] These variations may reflect the demographic variations in the types of CVD manifestations in PLWH.[43]

These results add to the growing body of evidence that demonstrates the increased burden of CVD in a population of PLWH that is aging.[5,44] Studies suggest that PLWH with 1 CVD risk factor had a hazard ratio of 2.0 for myocardial infarctions, and those with 3 or more factors had a hazard ratio of 3.6 compared with seronegative controls.[44] In our cohort, we found that patients with CVD were older, with a higher median hemoglobin A1C level and were less likely to be on ART. While median LDL-C levels were lower in the CVD group, this is likely due to the higher use of lipid-lowering medications in the CVD group. It should be noted that our cohort did not include seronegative controls, and we were thus unable to compare the relative associations of traditional risk factors and CVD between seropositive and seronegative individuals. In addition, our patient population had a larger proportion of individuals self-identifying as Black or African American and Hispanic compared with other published studies, which may make direct comparisons with other cohorts more difficult. However, the results of our study underscore the importance of addressing CVD risk factors in this demographic group.[2,45,46] Although gender was not a significant predictor of CVD in our cohort, other studies have shown

that HIV-positive females have a significantly higher risk of CVD compared with seronegative females.[47–49]

Some studies have demonstrated associations between ARTs and increased CVD risk.[16] In particular, protease inhibitors have been associated with dyslipidemia as well as increased fibrinogen levels.[20–22] Non-nucleoside reverse transcriptase inhibitors have also demonstrated an increase in total cholesterol and LDL-C in patients.[21] However, the START Trial showed that HIV-positive individuals on ART have a more favorable risk profile against CVD compared with those not on ART.[50] Our study showed that patients on ART therapy had a 63% reduction in the odds of having documented cardiovascular events, even when controlling for age, sex, diabetes, and smoking history (OR 0.37, 95% CI [0.19–0.74], $P = .005$, Supplemental Table 2, http://links.lww.com/MD/G247). This supports current knowledge that the HIV virus itself may contribute to an inflammatory cascade that promotes atherosclerosis irrespective of conventional CVD risk factors.[51,52] However, it is important to note in our study that while an undetectable viral load was associated with a lower odds of having documented CVD, this was not statistically significant in the univariate or multivariate models (OR 0.763, 95% CI [0.49–1.18], $P = .23$, Table 2). Our measurements of CD4 counts and viral loads were taken from the most recent clinic visit, and peak viral loads and CD4 troughs were not measured in this analysis. We cannot conclude from this study that the mechanism of the protective effect that ART has against CVD is through viral suppression. However, we can conclude that being on ART appears to overall be protective against CVD in PLWH.

Results of this study demonstrate a suboptimal utilization of antiplatelet and lipid-lowering agents for primary and secondary prevention of CVD among PLWH. A number of studies have reported underutilization of statin therapies for secondary prevention in the general population.[53–56] However, the phenomenon of underutilization of primary and secondary prevention is even more relevant for PLWH due to the enhanced CVD risk related to HIV.[37,57–62] Further, these results support existing data that report that use of aspirin for primary prevention is lower among ethnic minorities patients in the US.[63]

While a few small studies on the use of statins have shown reduction of subclinical inflammation and improved mortality in HIV,[64,65] a large randomized placebo-controlled trial (RE-PRIEVE) is underway and has completed enrollment to evaluate the impact of pitavastatin on reducing coronary atherosclerosis in PLWH on ART at low-moderate traditional risk for CVD.[66,67] One of the caveats of current strategies to reduce CVD risk in PLWH is that ASCVD scores have been shown to under-predict low-to-moderate coronary artery disease risk in these patients.[25,29,30] This paradoxical underestimation of risk was noted in our patient cohort, in which the calculated median 10-year risk of CVD of the entire cohort was lower than the actual prevalence of documented cardiovascular events (7.3% median ASCVD risk vs 10.4% CVD prevalence).

4.1. Limitations

The biggest limitation of the study is the cross-sectional design, which does not allow for temporal or trend analysis of risk factor profiles over time, the duration of exposure to specific ARTs, or duration of exposure to HIV. Additionally, there was no HIV-negative control group for comparison. The retrospective design of this study is susceptible to sampling bias, as we included only patients who were seen at a dedicated HIV clinic. Since the study was a retrospective chart review, our definition of CVD events was limited by what was documented in the medical record. There might have been additional cardiovascular events that were not documented. Additionally, documentation of lifestyle factors such as tobacco, alcohol, and drug use was determined by self-report during clinical encounters, which might have been biased. Finally, there might have been other confounding variables that we did not account for in the data collection and in the multivariate analysis. Although this retrospective study was conducted at a single center in Miami, FL, the analysis offers unique opportunities of studying often underrepresented patient populations (female, Black, Hispanic) that make up the large majority of new cases of HIV, according to the Center for Disease Control annual report.[34]

5. Conclusion

The advent of antiretroviral therapy has substantially improved survival in PLWH. However, CVD risk and rates of CVD are now high among PLWH who receive ART, especially with increasing age and HbA1c levels.[4] Yet, the use of medications for primary and secondary prevention is low. Therefore, interventions to increase awareness of CVD risk reduction strategies among provider of PLWH are needed to decrease the burden of CVD among this aging population. In addition, attitudes and beliefs regarding prevention of CVD should be explored for healthcare providers caring for PLWH, and strategies to overcome barriers to effective primary and secondary prevention, whether structural, cultural, or educational, should be explored to reduce CVD morbidity and mortality.

Author contributions

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Writing – review & editing: Fahim Pyarali, Roumen Iordanov, Bertrand Ebner, Louis Vincent, Claudia Martinez.

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