

# Factors Associated with Incident Cardiovascular Events and Cardiac Risk Assessment in a Cohort of HIV-infected Participants in Rio de Janeiro

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**Abstract:** *Background:* Cardiovascular events (CVEs) have emerged as an important cause of morbimortality in people living with HIV/AIDS (PLHA). We aimed to investigate factors associated with incident CVE and compare the observed incidence with the predicted CVE risk by three different equations. *Methods:* Among the 649 active participants of the INI-ELSA cohort, we analysed data of 644 individuals free of CVE at baseline examinations. We used Cox regression models to study factors associated with CVE and to assess the equation's performance we compared the observed incidence with the overall 5-year predicted risks. *Results:* Over a median follow-up of 6.26-years (interquartile range [IQR] 6.01-6.47), there were 18 CVE, four deaths. Overall, 57.92% were male, median age was 43.4 years (35.82-50.73), most were on cART (88.65%). Participants who had CVE were older, had poorer renal function, higher proportion of dyslipidemia and higher levels of systolic blood pressure and triglycerides. The observed CVE rate was 2.90% (1.60-4.90%) whereas their overall cardiovascular disease (CVD) risk differed depending on which score was used: 0.91 (0.42-20), 1.16 (0.38-2.78) and 1.68 (0.60-3.87), according to Framingham, ASCVD and DAD, respectively. In the multivariable Cox analysis black race, smoking 10+ packs years, dyslipidemia, current CD4 cell count  $\times 10^1$ , cumulative viral load and time on NNRTI were independent predictors of CVE. *Conclusion:* Both traditional and HIV-related factors were associated with incident CVE. Risk scores were inconsistent in classifying patients who had CVE as high risk, indicating that validation studies are required to improve risk assessment of PLHA in Brazil.

**Keywords:** Acquired Immunodeficiency Syndrome, Cardiovascular Disease, Risk Assessment

## 1. Introduction

Although in the last decades HIV infection and its related complications remained as the major causes of death in people living with HIV/AIDS (PLHA), mounting data suggest that cardiovascular disease (CVD) have emerged as important causes of morbimortality in PLHA, after the introduction of combined antiretroviral therapy (cART).

The etiology seems to be multifactorial; the main components of traditional CVD risk factors for the development of CVD are increasingly present in PLHA, as recent epidemiologic studies showed higher rates of diabetes, smoking and hypertension in PLHA when compared to the general population [1-4]. In addition, some cART regimens have been implicated in the induction of abnormal central fat accumulation, which in turn, promotes dyslipidemia and insulin resistance [5-7]. Consequently, HIV infection has been associated with 50% increase in myocardial infarction risk, even after controlling for well-known cardiovascular (CV) risk factors [8]. Although traditional risk factors do not fully explain the increased CVD risk, whether HIV infection is itself a risk factor by promoting immune activation and inflammation is not totally clear yet. Notwithstanding, it is of uppermost importance for clinicians to correctly recognize high-risk patients in order to initiate preventive interventions to control modifiable risk factors. To address this purpose, several risk functions have been derived from epidemiologic prospective studies in the general population. The most widely used in clinical practice, the Framingham risk score (FRS), was the first to demonstrate the ability to predict sex-specific 10-year CVD risk using a set of variables obtained from a Caucasian population, using a mathematical model [9]. Since then, it has been further validated for use in different populations, provided that adjustments are made for demographic variation and the underlying CVD rates [10, 11]. Recently, Framingham has been adopted for PLHA, generating criticism and debate in the literature about this approach, since PLHA hold unique characteristics [12-15]. The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) consortium developed a risk prediction equation specifically for PLHA, taking into account traditional and HIV-related CVD risk factors, and it was further updated to include a marker of immune function, even though its external validity is limited [16]. Lastly, the American College of Cardiology/American Heart Association (ACC/AHA) presented the Atherosclerotic Cardiovascular Disease Risk Score (ASCVD), whose difference is to include race to the algorithm, requiring further validation in external cohorts [17].

Accordingly, we previously reported that virologic suppression and higher CD4 counts were as important as traditional CVD risk factor for determining an incident cardiovascular events (CVE) among hospitalized PLHA of our cohort [18]. Nevertheless, there is scarce information in the literature about CVE incidence in PLHA who are followed in outpatient facilities in Brazil and the contribution of risk factors, either linked or not to HIV infection. This

information could improve clinical practice considering its contribution to a better approach driving preventive interventions for CVD risk reduction in PLHA. Therefore, we propose to investigate factors associated with incident CVE in PLHA in Brazil and secondarily to compare the predicted 5-year risk calculated by FRS, DAD and ASCVD with the observed CVE in our cohort.

## 2. Methods

The Instituto Nacional de Infectologia Evandro Chagas (INI) is a national reference center for infectious diseases, research, and training related to HIV/AIDS since 1986. An observational clinical database, available in electronic and paper records, is maintained, with PLHA receiving primary and tertiary HIV care at its facilities, which constitutes the INI cohort. Among the active participants of the INI cohort who were between the ages of 25 and 75 in 2011 ( $n=2,372$ ), 649 were randomly selected and invited to the INI-ELSA study, ELSA coming from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)[19]. Among those, 644 free of CVD at baseline visit were included in this study and prospectively followed until Dec 2017 for the occurrence of CVE.

### 2.1. Data Collection

Baseline visits consisted of the same examinations of the ELSA-Brasil, which aims to contribute relevant information with respect to the development and progression of chronic diseases, particularly cardiovascular and diabetes [20-23].

### 2.2. Baseline-visit

During the accrual period, between Jan 2011 and Dec 2011, participants underwent the ELSA-Brasil protocol workup, which included detailed interviews with standard questionnaires, covering sociodemographic characteristics, use of prescription and non-prescription medications in the last month and comorbidity characteristics [20]. In addition, an extensive workup including clinical and anthropometric examinations, oral glucose tolerance test; fasting venous blood samples were collected for a complete laboratory evaluation. Besides, regular information of INI cohort participants was also obtained from medical charts in the cohort's database, including use of cART, protease inhibitor (PI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and Nucleoside reverse transcriptase inhibitors (NRTI)-containing regimens and the length in years on each regimen, current CD4 counts, viral loads, cytomegalovirus (CMV) serology, nadir CD4 counts and previous HIV viral load measurements.

### 2.3. Follow-up Visits

Clinical events, whether or not associated with HIV/AIDS, antiretroviral treatment regimens and adverse events were systematically collected retrospectively from medical records. This work was carried out by a team of specialized and trained technicians, under the supervision of an

infectologist. HIV viral loads and CD4 + cell counts were measured every 4-6 months as part of regular outpatient care. Lymphocyte CD4 count was performed by flow cytometry (Becton-Dickinson, USA) and HIV viral load quantification is measured by the NUCLISENS methodology, with a minimum detection limit of 40 copies/ml.

#### 2.4. Outcome Definition

For the purposes of this study a CVE was defined as a composite of incident acute myocardial infarction (AMI), angina, stroke, heart failure or peripheral artery disease (PAD). In order to improve the quality of information, a systematic validation of patients who had CVEs recorded in their chart was performed by a cardiologist according to current guidelines [24-29]. Cardiovascular deaths that occurred in the study period were also monitored retrieving data from the coding causes of death in HIV (CoDe) system (<http://www.cphiv.dk/DAD/>). For the analysis, when a participant experienced an event of interest he was no more considered at risk.

#### 2.5. Covariables Definitions

Variables were defined or calculated as follows. Self-reported race/skin color was categorized into black, brown, white, and others. Diabetes mellitus (DM) was defined as having glycated hemoglobin > 6.5%, fasting glucose > 126 mg/dL, oral glucose tolerance test levels > 200 mg/dL or current use of a hypoglycemic drug. Resting blood pressure was measured three times in the non-dominant arm in the sitting position and hypertension was ascertained if the mean of the last 2 measurements showed systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg or if in use of anti-hypertensive drugs. Dyslipidemia was defined as low-density lipoprotein (LDL) levels  $\geq 130$  mg/dL or use of lipid-lowering drugs. Cumulative smoking was calculated as pack-years, by multiplying the number of packs smoked per day by the number of years of smoking. Family history of sudden death and family history of acute myocardial infarction (AMI) or stroke were defined as the informed occurrence of any episode of those conditions among parents or siblings younger than 65 years of age. Body mass index (BMI) was calculated as the ratio of measured weight in kilograms and squared height in meters. Cumulative viral load (VL; viremia copy-years) was defined as the area under the curve for two consecutive viral load measurements over time, in years [30]. Cumulative use of antiretroviral therapy was calculated as the sum of the difference between start and end dates of use up to the follow-up termination, in years. Estimated Glomerular filtration rate (eGFR) was calculated with the CKD-Epi equation.

#### 2.6. CVD Risk Equations

The predicted 5-year CVD risk was calculated for each participant at baseline using three CVD risk equations: 1) the FRS risk equation, calculated as a combination of age, sex, systolic blood pressure (SBP), antihypertensive therapy, serum total cholesterol (TC) and HDL-cholesterol (HDL-c) values,

current smoking status and diabetes. 2) The DAD CVD equation estimates risk by combining information for age; sex; SBP; serum TC and HDL-c, diabetes; smoking status; family history of CVD; current use of abacavir, indinavir, or lopinavir; and the number of years on indinavir or Lopinavir. 3) The ASCVD risk was estimated using age, diabetes, sex, race, smoking status, SBP, treatment for hypertension, TC and HDL-c. Then, for comparison proposes the 5-year risk of coronary heart disease was arbitrarily categorized as low (<1%), moderate (1 to 5%) and high (>5%) for each equation.

### 3. Statistical Analysis

Descriptive comparisons of general characteristics between groups, including predicted and observed CVE were done with Mann-Whitney tests for continuous and chi-squared or Fisher exact tests for categorical variables. Data were expressed as median [interquartile range](IQR) or frequency (%) where applicable. To study factors associated with CVE in PLHA, the best multivariable model among a set of candidate variables was chosen for Cox proportional hazards regression using a procedure implemented by a genetic algorithm, useful when we have a large candidate sets, and ranked by the Akaike information criterion. The procedure was also replicated 20 times and the overall best model was chosen through exhaustive screening. To assess the equations' performances, we compared the observed number of CVE with the absolute 5-year risk calculated by FRS, DAD and ASVCD. The observed number was adjusted for probability of event-free survival using the Kaplan-Meier (KM) estimator based on a tabulation of the number of PLHA at risk and the number of CVE at each unique time. For the times in which an event occurred, the probability of survival was estimated by the number of those who survived until that time over those who were at risk. The survival function estimated was the product of the probability of survival at each time and the adjusted observed number was the complement of that function. P-values less than 5% considered significant for differences between groups. All analyses were performed in the R environment version 3.2.2 [31].

### 4. Results

Among the 644 participants, followed for a median of 6.26-years (interquartile range [IQR] 6.01-6.47), there were 18 CVE: 6 (33.33%) acute myocardial infarctions, 2 (11.11%) strokes, 6 (33.33%) unstable anginas and 4 (22.23%) cardiovascular deaths. The event rate was 4.46/1000 person-years (4031 person-years of follow-up), yielding a cumulative five-year survival rate of 97.1% (95%CI=95.8-98.4). Overall, 57.92% were male, predominantly brown (40.53%), and the median age was 43.4 (35.82-50.73) years. Among traditional CV risk factors, smoking was found in 23.45%, dyslipidemia in 37.24%, hypertension in 31.06% and diabetes in 25.47%. Participants who suffered a CVE were older (median age 51.66 years), had higher levels of triglycerides and dyslipidemia, with a decreased glomerular filtration rate estimated by CKD-Epi (median 91.52 mL/min per 1.73m<sup>2</sup>). The main clinical and laboratory

characteristics of the study participants with or without CVE are shown in Table 1. Regarding HIV-related characteristics, at baseline most of them were under cART (88.65%) for a median time of 9.82 years (6.3-16.32) with undetectable viral load (71.27%) and high levels of current CD4 cell counts (median 540 [IQR=371-739.25]) and the most commonly used regimen

was NRTI (81.68%). The median of current lower CD4 cell count at baseline visit was significantly lower and the cumulative viral load was higher in participants who had a CVE, when compared to those who did not; cART regimens and HIV-related characteristics of PLHA are depicted in Table 2.

**Table 1.** General characteristics of PLHA according to the incidence of cardiovascular event.

	Groups			
	CVE-	CVE+	Total	p value <sup>b</sup>
Total	626	18	644	
Sex: Male	361 (57.67)	12 (66.67)	373 (57.92)	0.4458
Age in years – median (IQR)	43.13 (35.8, 50.16)	51.66 (47.66, 53.84)	43.4 (35.82, 50.73)	0.0091
Schooling: <9 years	296 (47.28)	10 (55.56)	306 (47.52)	0.4884
Race				0.7105
Black	141 (22.52)	6 (33.33)	147 (22.83)	
Brown	254 (40.58)	7 (38.89)	261 (40.53)	
White	205 (32.75)	5 (27.78)	210 (32.61)	
Others	26 (4.15)	0 (0)	26 (4.04)	
Smoking				0.5448
Never	316 (50.48)	7 (38.89)	323 (50.16)	
Former	165 (26.36)	5 (27.78)	170 (26.4)	
Current	145 (23.16)	6 (33.33)	151 (23.45)	
Pack. years (10+)	163 (26.08)	8 (44.44)	171 (26.59)	0.1027
Income (R\$) – median (IQR)	414.5 (207.25, 1036.25)	414.5 (207.25, 880.81)	414.5 (207.25, 1036.25)	0.3659
Family History of Sudden Death	118 (18.85)	2 (11.11)	120 (18.63)	0.549
Family History of AMI or Stroke	173 (27.64)	2 (11.11)	175 (27.17)	0.1776
Total cholesterol (mg/dL) – median (IQR)	181 (155.25, 210.75)	202.5 (171.25, 226.75)	182 (156, 211)	0.1551
HDL (mg/dL) – median (IQR)	42 (35, 52)	42 (32.5, 51.75)	42 (35, 52)	0.7244
LDL (mg/dL) – median (IQR)	106 (87, 133)	108 (94, 131)	106 (87, 133)	0.5887
Triglycerides (mg/dL) – median (IQR)	119 (84, 181)	192.5 (165.75, 243.75)	120 (85, 184.5)	<0.001
Dyslipidemia	224 (36.48)	11 (64.71)	235 (37.24)	0.0176
Use of lipid-lowering drugs	81 (12.94)	7 (38.89)	88 (13.66)	0.0063
Hypertension	191 (30.51)	9 (50)	200 (31.06)	0.0781
Antihypertensive medication use	138 (22.04)	5 (27.78)	143 (22.2)	0.5675
DM	157 (25.08)	7 (38.89)	164 (25.47)	0.181
Use of antidiabetic drugs	32 (5.11)	3 (16.67)	35 (5.43)	0.0684
Waist/hip ratio – median (IQR)	0.9 (0.84, 0.96)	0.94 (0.88, 0.98)	0.9 (0.84, 0.96)	0.0631
BMI – median (IQR)	24.45 (21.99, 27.37)	23.6 (21.39, 28.18)	24.43 (21.93, 27.51)	0.8628
hs-CRP (mg/dL) – median (IQR)	0.29 (0.17, 0.64)	0.27 (0.21, 0.96)	0.29 (0.17, 0.65)	0.5358
CKD-Epi – median (IQR)	106.89 (93.22, 121.25)	91.52 (77.75, 112.62)	106.78 (92.7, 121.04)	0.0138
SBP – median (IQR)	118 (110, 129)	126.75 (111.5, 141.62)	118 (110, 129)	0.0757
DBP – median (IQR)	76.75 (70.5, 83.38)	79.5 (73.5, 91.62)	77 (70.5, 83.5)	0.1554

<sup>a</sup> Columns provide numbers (%) and interquartile range (IQR) where applicable

<sup>b</sup> Mann-Whitney and Chi-Square tests

Abbreviations: IQR – interquartile range; AMI – acute myocardial infarction; CVE – cardiovascular event; BMI – body mass index; DM – diabetes mellitus; HDL – high density lipoprotein; LDL – low density lipoprotein; hs-CRP high sensitivity C-reactive protein; CKD-Epi – Chronic Kidney Disease Epidemiology Collaboration equation; SBP – systolic blood pressure; DBP – diastolic blood pressure

Multivariable Cox regression analysis showed that self-reported black race/color (hazard ratio [HR]=7.96, 95%CI=1.74; 36.48,  $p=0.007$ ), smoking 10+ packs years (HR=4.05, 95%CI=1.22; 13.42,  $p=0.02$ ), dyslipidemia (HR=6.09, 95%CI=1.85; 19.98,  $p<0.01$ ), cumulative viral load (HR=1.06, 95%CI=1.02; 1.10,  $p<0.01$ ) and time on NNRTI (HR=1.24, 95%CI=1.07; 1.48,  $p<0.01$ ), were independent predictors of increased CVE whereas time on NRTI in years (HR=0.77, 95%CI=0.65; 0.91,  $p<0.01$ ) and every 10 units increase in current CD4 cell count (HR=9.97, 95%CI=9.94; 9.99,  $p=0.01$ ) had a protective effect (Table 3).

#### Estimated CVD risk equations

The estimated 5-year interquartile range risk varied between 0.6% and 3.87%, with a median of 1.68% based on the DAD

equation, from 0.42 to 2% with a median of 0.91% based on the FRS and from 0.38 to 2.78% with a median of 1.16% based on the ASCVD calculator, whereas the observed 5-year KM adjusted CVE was 2.90% (95%CI=1.6-4.90%) (Figure 1). Overall, the categorized 5-year risk showed that DAD, FRS and ASCVD equations estimated 17.46%, 4.84% and 13.73% of the study population to be at high risk, respectively. Among those who had a CVE, the DAD equation had higher 5-year median values (4.05 [IQR=2.33-5.6]), when compared to FRS (2.43 [IQR=1.32-3.31]) and to ASCVD calculator (2.73 [IQR=1.49-5.35]), and both DAD and ASVCD classified a larger proportion as high risk (33.33%) than FRS (5.56%). The overall absolute 5-year CVE risk estimates and the risk categories of DAD, FRS and ASVCD equations in PLHA are exhibited in Table 4.

**Table 2.** *cART regimens and HIV-related characteristics of PLHA by incidence of CVE.*

	CVE-	CVE+	Total	p-value <sup>b</sup>
Total	626	18	644	
cART use: Yes	554 (88.64)	16 (88.89)	570 (88.65)	0.99
PI-containing regimen	326 (52.08)	11 (61.11)	337 (52.33)	0.4493
NNRTI-containing regimen	407 (65.02)	12 (66.67)	419 (65.06)	0.8849
NRTI-containing regimen	510 (81.47)	16 (88.89)	526 (81.68)	0.5502
Cumulative Viral Load—median (IQR)	15.12 (6.88, 29.46)	31.58 (9.66, 42.02)	15.28 (7, 29.84)	0.0492
Current CD4 counts (cells/mL)—median (IQR)	540.5 (374, 740.75)	407.5 (230, 595.75)	540 (371, 739.25)	0.0404
Nadir CD4 counts (cells/mL)—median (IQR)	216 (99, 316)	190 (34, 237)	214.5 (96.25, 314.75)	0.0672
Undetectable Viral Load: Yes	441 (71.24)	13 (72.22)	454 (71.27)	0.928
Time on cART (years)—median (IQR)	9.78 (6.27, 16.27)	11.05 (7.16, 16.08)	9.82 (6.3, 16.32)	0.6297
Time on PI (years)—median (IQR)	4.66 (0, 11.15)	9.03 (0.99, 13.12)	4.69 (0, 11.26)	0.2482
Time on NNRTI (years)—median (IQR)	3.18 (0.08, 6.8)	2.54 (0, 8.69)	3.18 (0.07, 6.84)	0.9421
Time on NRTI (years)—median (IQR)	8.88 (5.79, 15.96)	10.08 (6.38, 14.37)	8.88 (5.8, 15.95)	0.9326

<sup>a</sup> Columns provide numbers (%) and interquartile range (IQR) where applicable

<sup>b</sup> Mann-Whitney and Chi-Square tests

Abbreviations: cART — combined antiretroviral therapy; PI—protease inhibitors; NNRTI— Non-nucleoside reverse transcriptase inhibitors, NRTI - Nucleoside reverse transcriptase inhibitors

**Table 3.** *Final Cox model for clinical predictors of CVD in in people living with HIV/AIDS.*

Variable	HR	95%IC	p-value
Sex: Male	0.858	0.274; 2.686	0.7929
Age in years	0.999	0.935; 1.067	0.9822
Race			
Black	7.962	1.737; 36.485	0.0076
Brown	2.360	0.540; 10.303	0.2534
Pack. years (10+)	4.053	1.224; 13.420	0.0220
Family History of AMI or Stroke	0.137	0.023; 0.792	0.0264
Dyslipidemia	6.086	1.853; 19.985	0.0029
Diabetes Mellitus	2.773	0.935; 8.219	0.0658
Current CD4+ cell count (10 <sup>3</sup> )	9.97	9.94; 9.99	0.0195
HDL (mg/dL)	1.001	0.954; 1.048	0.9857
CKD-Epi	0.957	0.932; 0.982	0.0009
Cumulative Viral Load	1.062	1.023; 1.101	0.0013
Time on NNRTI (years)	1.257	1.070; 1.476	0.0052
Time on NRTI (years)	0.770	0.650; 0.913	0.0026
Time on IP (years)	1.128	0.985; 1.292	0.0816

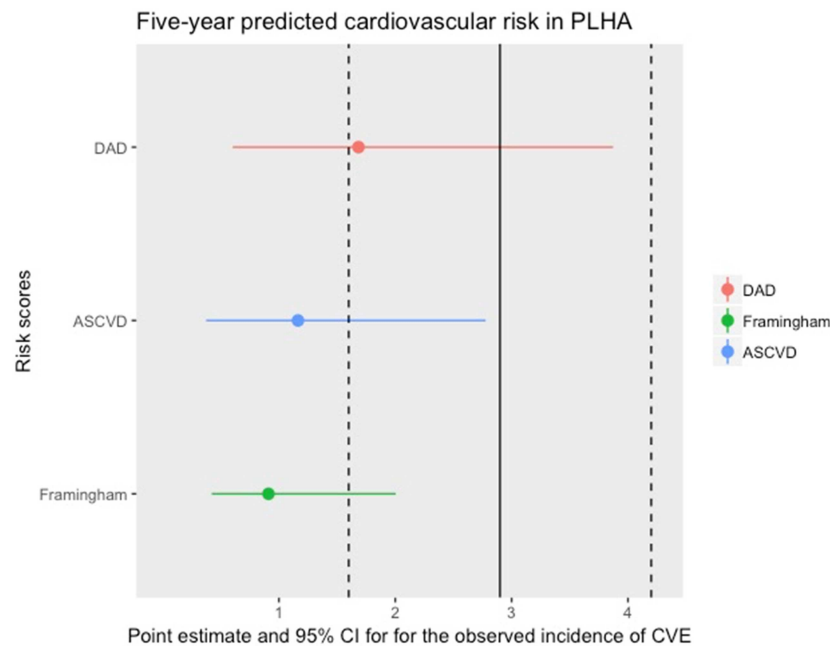
Abbreviations: CVE – cardiovascular events; DM – diabetes mellitus; cART — combined antiretroviral therapy; PI—protease inhibitors; NNRTI— Non-nucleoside reverse transcriptase inhibitors, NRTI - Nucleoside reverse transcriptase inhibitors

**Table 4.** *Absolute CVD risk scores and categories of DAD, FRS and ASCVD equations in people living with HIV/AIDS.*

	Groups			p value <sup>b</sup>
	CVE-	CVE+	Total	
Total	610	11	621	
DAD 5 years median (IQR)	1.6 (0.58, 3.69)	4.05 (2.33, 5.6)	1.68 (0.6, 3.87)	<0.001
DAD 5 years categorized				
High	104 (16.99)	6 (33.33)	110 (17.46)	0.0302
Moderate	264 (43.14)	10 (55.56)	274 (43.49)	
Low	244 (39.87)	2 (11.11)	246 (39.05)	
FRS 5 years median (IQR)	0.89 (0.41, 1.96)	2.43 (1.32, 3.31)	0.91 (0.42, 2)	0.0013
FRS 5 years categorized				0.0076
High	30 (4.82)	1 (5.56)	31 (4.84)	
Moderate	261 (41.89)	14 (77.78)	275 (42.9)	
Low	332 (53.29)	3 (16.67)	335 (52.26)	
ASCVD 5 years median (IQR)	1.14 (0.35, 2.69)	2.73 (1.49, 5.35)	1.16 (0.38, 2.78)	0.0024
ASCVD 5 years categorized				0.0049
High	82 (13.16)	6 (33.33)	88 (13.73)	
Moderate	258 (41.41)	10 (55.56)	268 (41.81)	
Low	283 (45.43)	2 (11.11)	285 (44.46)	

<sup>a</sup> Abbreviations: Framingham Risk Score (FRS), Data Collection on Adverse Events of Anti-HIV Drugs (D: A: D) and Atherosclerotic Cardiovascular Disease Risk Score (ASCVD); Columns provide numbers (%) and interquartile range (IQR) where applicable

<sup>b</sup> Mann-Whitney and Chi-Square tests



**Figure 1.** The five year predicted cardiovascular risk in people living with HIV/AIDS.

The x-axis shows the point estimate (solid line) and 95% confidence interval (dashed lines) for the observed incidence of cardiovascular events (CVE). In the Y-axis are the predicted probabilities (median and interquartile range) for The Data Collection on Adverse Events of Anti-HIV Drugs (DAD), Atherosclerotic Cardiovascular Disease (ASCVD) and Framingham risk score.

## 5. Discussion

In this study we showed that traditional CV risk factors and HIV-specific characteristics were independent predictors of CVE in PLHA, whereas higher CD4 counts were cardioprotective. Moreover, the DAD equation seems to better predict CVE in a Brazilian cohort of PLHA, compared to other two widely used ones.

Our main findings are in agreement with several studies. For instance, De Socio et al recently found age, smoking and diabetes as predictors of CVE in PLHA [32]. For Quiros et al., in a population-based study of PLHA in northern Italy, age greater than 45 years, male gender, diabetes, and total cholesterol were significantly associated with CVE [33].

It is noteworthy that the magnitude of effect for black race was substantial as a predictor of CVE. Aside from genetic and environmental influences, lifetime risk of CVE in the general population is dependent on the burden of risk factors jointly present. Thereupon, epidemiological studies reveal higher prevalences of hypertension, diabetes and obesity in African Americans than whites [34-36]. In the Brazilian setting, participants of black race from the ELSA-Brasil study had poorer metrics of cardiovascular related health and lifestyle factors, along with early detection of atherosclerosis but it was not possible to establish an association between racial discrimination and hypertension [37-39]. Furthermore, there has been evidence of racial disparities in cardiovascular health care utilization and treatments that would lead to adverse clinical outcomes [40, 41]. Altogether, it might be that the same mechanisms that cause blacks to have a higher

occurrence of cardiovascular disease are operating in people living with HIV as well.

We also detected a strong association between smoking 10+ packs years and CVE. Phan B et al found similar results, where baseline carotid plaque was independently associated with pack per year of smoking [42] and for Hsue PY et al, cigarette pack-years was a predictor of intima-media thickness [43]. These results, coupled with epidemiologic studies that show rates of smoking two to three times higher among PLHA than age-matched controls [44, 45], reinforce the importance of strategies to stop smoking and its gains in primary prevention.

The HIV-induced proinflammatory state may contribute to the overall increased number of CVE in PLHA, particularly in those not on ART [46]. In this scenario of cART use our results showed that higher levels of current CD4 was cardioprotective and in the unadjusted analysis we observed that parameters of immune activation and viral activity such as current CD4 cell count and undetectable viral load were in optimal conditions as a consequence of HIV treatment. We suppose that the large proportion of cART use (88.39%) in our cohort had a relevant role in inducing control of chronic inflammation and vascular damage as potential pathogenic mechanisms, promoting an indirect effect in CVE rate reduction. This hypothesis is corroborated by data from SMART and ESPRIT randomized clinical trials, whose cART arms included patients with well-controlled viral loads and high CD4 counts, and showed mortality rates comparable to the general population. In these studies, the most frequent cause of death was CVD [47].

We also found that viremia copy-years or cumulative viral

load was associated with increased CVD. The cumulative viral load means a person had a detectable viral load for progressively longer times, inducing chronic inflammation. Epidemiologic studies suggest that keeping viral load consistently undetectable with cART reduces the risk of a cardiovascular event [48, 49]. For instance, in the SMART study, cART interruption was associated with increased CVD, mainly as consequence of lowering CD4<sup>+</sup> cell count and increasing viral load [50].

Collectively these data suggest a tangible benefit of continuous use of cART having virologic control as the underlying goal. Herein, it is fundamental the implementation of regular monitoring of comorbidities related to CVD as well as assessment of interventions and lifestyle modification following the current guidelines as part of the HIV care continuum, to further lower CV risk.

Regarding the performance of the absolute risk estimated by the three equations in our exploratory analysis, although all of them underestimated the observed risk, the DAD score performed better (1.44%) than FRS (0.88%) and ASVCD (1.13%) when we compared these point estimates with the observed 5-year CVE (1.80%). It is also important to notice that the three predicted risks are within the confidence interval width estimated for this population sample (Figure 1), but only the DAD score range included the point estimate of the observed risk. We found discordant results in the literature when assessing CVD prediction in PLHA; for instance, Thompson et al. found that DAD and ASVCD underestimated the CV risk whereas FRS accurately predicted it [51]. In accordance, De Socio observed that CVE were well predicted by FRS [32], whereas for Raggi et al., both ASVCD and FRS estimates for 10 years and DAD estimates for 5 years, have similar risks of CVE and the author concluded that all equations showed modest predictive ability [52]. More recently, Crane et al reported in a conference abstract that ASCVD had better discrimination than other 3 risk scores, including the DAD and FRS for myocardial infarction in PLHA [53]. The reasons for these conflicting results could be partially explained by the use of surrogate endpoints to measure CVE and differences in relation to demographic characteristics and CVE definition or its ascertainment among the populations in these studies.

Our results suggest that FRS could be underestimating CVE risk in PLHA in Brazil, as the predicted 5-year absolute CVD risk was the lowest amongst the three equations that have been evaluated and models that take into account exposure to individual cART regimens and immune activation could more accurately predict CVE occurrence. However, to better understand these inconsistencies, formal validation of these models are necessary to determine whether one of these tools can be generalized among PLHA in Brazil.

Moreover, when we consider the absolute 5-year risk calculated by the updated DAD equation in the original cohort and the calculated risk by DAD equation in our cohort there is a considerable difference on the predicted risks (2.49% vs.

1.44%), highlighting the baseline demographic imbalances between these populations.

The limitations of this study include the selection of a random sample from the INI Cohort, instead of using data for all the participants, due to logistic and budgetary limitations. Even though a specialist and a training doctor did the classification of CVE blinded to exposure status, it is possible that some degree of nondifferential CVE misclassification could have occurred; moreover, we did not search our database for individuals who were considered CVE-free, but actually had the outcome, which could have changed our estimates towards the null hypothesis. Another limitation is the small number of CVE, decreasing the precision of the results. Although we have calculated the ASCVD including patients who were using statins the score was originally derived to guide statins initiation and therefore we could assume that the risk in this participants taking statins was even lower. The strengths of the study include a well-defined cohort along with a complete high-quality dataset of covariables and no losses of follow up, reducing the role of potential confounders, increasing internal validity. Furthermore, we independently validated the CVE classification, improving accuracy of CVE diagnosis obtained from our medical charts.

To the best of our knowledge, this is the first study to investigate incidence and factors associated with CVE, assessing its risk by three different equations in a middle-income country.

## 6. Conclusion

Traditional modifiable CV risk factors, including smoking 10+ packs year, dyslipidemia and renal function are still major independent predictors of CVE in PLHA, and strategies towards controlling those risk factors along with smoking cessation are essential for primary prevention. It is also critical to implement public policies to mitigate health inequalities among Blacks. Continuous cART use should be reinforced in order to achieve viral suppression and consequently CVE reduction. The DAD equation seems to better predict CVE in PLHA than FRS and ASCVD; however, future studies should perform a formal validation of these tools in Brazil.

## Data Availability

Due to legal and ethical restrictions prohibiting public sharing of data, only a portion of what was used in order to replicate all study findings and the supporting conclusions, will be available upon request.

## Conflict of Interest

The authors have no conflict of interest to declare.

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