Cardiovascular disease among people living with HIV in Brazil

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Abstract

Objectives: There is a paucity of data on cardiovascular disease (CVD) among people living with HIV (PLHIV) in resource-limited countries. We assessed factors associated with CVD and the impact of prevalent CVD on all-cause mortality in PLHIV on antiretroviral therapy in Brazil.

Methods: Competing risk-regression to assess factors associated with CVD and all-cause mortality in the HIV-Brazil Cohort Study between 2003-2014.

Results: Among 5,614 patients, the rate of CVD was 3.5 (95% confidence interval [95%CI] 2.9-4.3) per 1,000 person years. CVD was associated with older age (adjusted hazard ratio [aHR] 6.4 for ≥55 years versus <35 years, 95%CI 2.5-16.3, p<0.01), black race (aHR 1.8 versus white race, 95%CI 1.0-3.1, p=0.04), past CVD (aHR 3.0 versus no past CVD, 95%CI 1.4-6.2, p<0.01), hypertension (aHR 1.8 versus no hypertension, 95%CI 1.0-3.1,

p=0.04), high-grade dyslipidemia (aHR 9.3 versus no high-grade dyslipidemia, 95%CI 6.0-14.6, p<0.01), ever smoking (aHR 2.4 versus never, 95%CI 1.2-5.0, p=0.02), and low nadir CD4 cell count (aHR 1.8 for 100-250 cells/mm^3 versus >250 cells/mm^3, 95%CI 1.0-3.2, p=0.05). The rate of death was 16.6 (95%CI 15.1-18.3) per 1,000 person years. Death was strongly associated with having had a past CVD event (aHR 1.7 versus no past CVD event, 95%CI 1.1-2.7, p=0.01).

Conclusions: Traditional and HIV-specific factors associated with CVD among PLHIV in Brazil are similar to those identified among PLHIV in high-income countries. PLHIV in Brazil with a history of CVD have a high risk of death. CVD care and treatment remain priorities for PLHIV in Brazil as this population ages and antiretroviral therapy use expands.

Keywords: HIV; Cardiovascular disease; Mortality; Brazil; Antiretroviral therapy

Introduction

Studies from high-income countries have shown that people living with HIV (PLHIV) have about a two-fold increased risk of cardiovascular disease (CVD) compared to their HIV-uninfected peers.[1] However, there is a paucity of data on CVD among PLHIV in resource-limited countries.[2-4]

Brazil is an important country in which to study long-term health outcomes among PLHIV, given its early availability of antiretroviral therapy (ART). Like many other middle-income countries, the prevalence of CVD and other non-communicable diseases in Brazil is increasing in the general population.[5-8] Despite this, recent evidence from the HIV-Brazil Cohort Study suggests CVD incidence has plateaued among PLHIV.[9] Clinical factors that may be influencing this trend have not been described. Further, it is uncertain to what extent past CVD is a risk factor for mortality among PLHIV in Brazil. In the general population [10-12] and among PLHIV [13] in high-income settings, past CVD has been shown to approximately double the risk of all-cause mortality.

We sought to address these knowledge gaps. Determining key factors associated with CVD and the influence of past CVD on all-cause mortality among PLHIV in Brazil will aid the allocation of healthcare resources and allow policy makers and researchers to estimate the effectiveness of potential CVD prevention methods in this population.

Methods

Study Population

We used data collected between January 2003 and December 2014 from seven HIV clinics with validated CVD outcomes in the HIV-Brazil Cohort Study, a longitudinal cohort study of adults initiating ART.[14] The sites involved were São Paulo State Department of Health STD/AIDS Referral and Training Center, São Paulo; Professor Edgard Santos University Hospital, Salvador; National Institute on Infectology Evandro Chagas - Fiocruz, Rio De Janeiro; Hospital Sanatório Partenon, Porto Alegre; Municipal Specialized Treatment Facility, San Jose Rio Preto; Santana Municipal Network, São Paulo; and Federal University of Minas Gerais, Belo Horizonte.

Ethics

The HIV-Brazil Cohort Study protocol was approved by the Institutional Review Boards of participating sites according to the Brazilian regulation for research with human subjects. Written informed consent was waived for retrospectively collected data, however, all enrolled patients provided written informed consent to contribute prospectively collected data.

Inclusion Criteria

Patients were included in our CVD analysis if they had documentation of at least one day of follow-up on ART. Our mortality analysis focused on characterizing the impact of prior CVD in patients' stable on ART (defined as having been on ART for at least six months) so that our results would not be dominated by the high rate of AIDS-associated mortality early after ART initiation.[15] Patients included in the CVD analysis who had, or developed, a history of CVD were included in the mortality analysis from the date of their first CVD event or six months after ART initiation, whichever came last, alongside those in the CVD analysis who did not experience a CVD event who were included from six months after ART initiation.

Definitions

Baseline for our CVD analysis was defined as the date of ART initiation, and baseline for our mortality analysis was defined as six months after ART initiation or the date of first CVD event, whichever came last (six months after ART initiation was defined as baseline for those without documentation of a CVD event). ART was defined as three or more antiretroviral drugs in a single regimen. The window period for baseline CD4 cell count, CD4/CD8 ratio, and HIV viral load was between baseline and six months before baseline. When more than one measurement was available in the window period, the measurement taken closest to baseline was

used. Nadir CD4 cell count was defined as the lowest CD4 cell count documented prior to ART initiation. Time-updated data was not available on smoking status, but we were able to define patients as ever or never having smoked based on information documented at ART initiation.

CVD was defined as non-fatal myocardial infarction, cardiac ischemia, angina, coronary artery disease, angioplasty, non-fatal stroke, or transient ischemic attack. Cause of death information was not available and therefore we were unable to include fatal myocardial infarction or fatal stroke in our CVD definition. CVD, diabetes (fasting blood glucose ≥ 126mg/dL, random blood glucose ≥ 200mg/dL, or hemoglobin A1c > 6.5%) and high-grade dyslipidemia (total cholesterol ≥ 300mg/dL, low-density lipoprotein ≥ 190mg/dL, or triglyceride > 500mg/dL) diagnoses were validated by chart review performed by clinicians at contributing sites. Events were "confirmed" where a definitive medical report, such as a laboratory report or radiographic report, was present along with documentation of the diagnosis in the medical record. Events were defined as "probable" when there was a documented diagnosis in the medical record supported by the initiation of treatment for that diagnosis or medical test data, or the diagnosis being cited as probable in a consultation note, hospital discharge summary, or autopsy report. Events were "possible" when a diagnosis was based on clinical exam without further investigation, or the patient self-reported a diagnosis with evidence of receiving appropriate treatment. We included all levels of certainty as a positive diagnosis. Hypertension diagnoses were not validated; however, positive diagnoses were defined as confirmed systolic blood pressure >140 mmHg, confirmed diastolic blood pressure >90 mmHg, treatment with an antihypertensive drug, or documentation of a positive diagnosis in the medical record.

Loss to follow-up was defined as the absence of patient contact for more than 12 months and failure to identify the patient in the national death registry, as described in [14].

Statistical Analysis

Cumulative incidence plots and competing risk-regression were used to assess factors associated with CVD and all-cause mortality. In the CVD analysis, follow-up was censored at the last recorded clinic visit, and loss to follow-up and death were considered competing events. In the mortality analysis, follow-up was censored at the last recorded clinic visit, and loss to follow-up was considered a competing event. Follow-up time was left truncated in the mortality analysis so that patients who developed CVD after six months of ART would begin contributing time on ART from a point consistent with their total duration of ART use at that time rather than from the origin.

Sex, race, mode of HIV exposure, past CVD, smoking status at ART initiation, nadir CD4 cell count at ART initiation, AIDS diagnosis prior to ART initiation, year of ART initiation, and HIV clinic were analyzed as fixed covariates. Age, hypertension, dyslipidemia, diabetes, CD4 cell count, CD4/CD8 ratio, HIV viral load, abacavir use, and protease inhibitor use were evaluated as time-updated covariates. We focused our evaluation of ART in the CVD analysis on abacavir and protease inhibitors as both have previously been found to be associated with CVD.[16-18]

All evaluated co-variates were included in our multivariate models unless there was substantial correlation detected between co-variates, in which case only the most statistically significant co-variate was retained. We did not include nadir CD4 cell count, CD4 cell count, or CD4/CD8 ratio together in our multivariate analyses given the clinical similarity of these measures. For simplicity, we have labeled sub-distribution hazard ratios generated from our competing risk-regression models as hazard ratios (HRs). Patients with missing data were included in all analyses, but we do not report HRs for missing categories.

Many studies of CVD in PLHIV have excluded patients with a history of CVD at ART initiation.[2,16,18-20] We did not make this exclusion to make our results as relevant as possible to physicians managing the CVD risk of all presenting PLHIV. Nevertheless, in the interest of making our results more directly comparable with those of others, we conducted an alternate CVD analysis whereby PLHIV with existing CVD at ART initiation were excluded.

All data management was conducted with SAS 9.4 (SAS Institute, Inc, Cary, North Carolina) and all statistical analyses with Stata 14 (Stata Corp., College Station, Texas).

Results

Of 6,204 patients included in the HIV-Brazil Cohort Study, 5,614 (90.5%) had at least one day of follow-up on ART. Of these, 96 (1.7%) experienced a CVD event after ART initiation; 58 events were due to coronary artery dysfunction and 38 events were due to cerebrovascular dysfunction. The overall rate of CVD was 3.5 (95% confidence interval [95%CI] 2.9-4.3) per 1,000 person years. Rates of coronary artery dysfunction and cerebrovascular dysfunction were 2.1 (95%CI 1.6-2.7) and 1.4 (95%CI 1.0-1.9) per 1,000 person years, respectively. There were 5,381 patients with more than six months of follow-up on ART who were included in our mortality analysis, among whom 418 (7.8%) died during follow-up. The overall rate of death was 16.6 (95%CI 15.1-18.3) per 1,000 person years. Table 1 displays the baseline characteristics of both our CVD analysis population and our mortality analysis population. The rate of loss to follow-up in our CVD analysis

was 4.4 (95%CI 3.6-5.2) per 1,000 person years and in our mortality analysis it was 4.5 (95%CI 3.7-5.4) per 1,000 person years.

CVD was associated with both traditional and HIV-specific risk factors (Figure 1 and Table 2). Traditional risk factors included older age (adjusted HR [aHR] 6.4 for ≥55 years versus <35 years, 95%CI 2.5-16.3, p<0.01), black race (aHR 1.8 versus white race, 95%CI 1.0-3.1, p=0.04), past CVD (aHR 3.0 versus no past CVD, 95%CI 1.4-6.2, p<0.01), hypertension (aHR 1.8 versus no hypertension, 95%CI 1.0-3.1, p=0.04), high-grade dyslipidemia (aHR 9.3 versus no high-grade dyslipidemia, 95%CI 6.0-14.6, p<0.01) and ever smoking (aHR 2.4 versus never, 95%CI 1.2-5.0, p=0.02). The main HIV-specific risk factor was lower nadir CD4 cell count (aHR 1.8 for 100-250 cells/mm^3 versus >250 cells/mm^3, 95%CI 1.0-3.2, p=0.05). Other immune markers, HIV viral load, abacavir use, and protease inhibitor use were not significantly associated with CVD. Similar results were seen in our alternate model excluding PLHIV with existing CVD at ART initiation, although CVD rates were generally lower (Supplementary Figure 1 and Supplementary Table 1).

Figure 2 and Table 3 show that death on ART was strongly associated with having had a past CVD event (aHR 1.7 versus no past CVD event, 95%CI 1.1-2.7, p=0.01). Other predictive factors included older age (aHR 2.0 for ≥55 years versus <35 years, 95%CI 1.4-3.0, p<0.01), male sex (aHR 1.3 versus female, 95%CI 1.0-1.6, p=0.05), mixed black race (aHR 1.3 versus white race, 95%CI 1.0-1.7, p=0.02), exposure to HIV via intravenous drug use (aHR 1.7 versus heterosexual exposure, 95%CI 1.2-2.5, p<0.01), diabetes (aHR 1.6 versus no diabetes, 95%CI 1.1-2.2, p=0.02), low CD4 cell count (aHR 7.7 for <200 cells/mm^3 versus >500 cells/mm^3, 95%CI 5.6-10.6, p<0.01), low CD4/CD8 ratio (aHR 2.5 for <0.4 versus >0.7, 95%CI 1.8-3.4, p<0.01), detectable HIV viral load (aHR 2.1 versus undetectable, 95%CI 1.7-2.7, p<0.01), and earlier year of ART initiation (aHR 1.5 for 2000-2004 versus 2010-2014, 95%CI 1.0-2.1, p=0.04). There were also significant differences in mortality rate among HIV clinics (see Table 3).

Discussion

CVD events occur in approximately 0.35% of PLHIV per year in Brazil. We found events were associated with both traditional and HIV-specific risk factors. Further, we have shown that a history of CVD increases the hazard of all-cause mortality by approximately 70% among PLHIV in Brazil.

Earlier work from the Data collection on Adverse events of Anti-HIV Drugs (D:A:D) cohort, which follows PLHIV in Europe, the US, Australia and Argentina, found CVD occurred at a rate of 5.4 per 1,000 person years.[16] This cohort was of a similar age to ours but the analysis included fatal CVD events and coronary artery

bypass graft in the definition of CVD, neither of which were in our definition. This may explain why we found a lower rate of CVD. Globally, estimated crude rates of myocardial infarction and stroke among PLHIV are consistent with our findings for Brazil.[1] Unfortunately however, data from resource-limited countries are scarce. In a single-center study conducted in Rio de Janeiro, in which a broad definition of CVD was employed (any death or hospitalization associated with heart or vascular disease, ischemic heart disease, stroke, venous thromboembolism, or pulmonary embolism), the incidence of CVD among 2,960 PLHIV was 6.8 per 1,000 person years.[2] Among a cohort involving HIV clinics in high- and middle-income Asian countries, Bijker et al found a CVD event rate of 2.2 per 1,000 person-years.[3] The authors of the Asian study suggest their low CVD rate may be explained by underdiagnosis of CVD. In lower resource settings, limited accessibility of screening and diagnostic tools may result in high rates of missed CVD diagnosis. Moreover, HIV-associated stigma has been described as a major barrier to healthcare utilization among PLHIV in resource-limited settings.[21] Given our CVD event rate for Brazil was comparable to rates reported from high-income areas, it may be that true rates of CVD and rates of missed diagnosis are similar for PLHIV in these settings. Alternatively, this finding could also be explained by a high true rate of CVD in Brazil being met by high rates of missed diagnosis.

The traditional risk factors we found associated with CVD in PLHIV were similar to those reported in earlier studies from high-income and resource-limited settings.[2,3,16,19] Consistent with our findings, Diaz et al also found that low nadir CD4 cell count was associated with CVD among PLHIV in Rio de Janeiro.[2] Low CD4 levels and detectable viral load are linked to chronic immune activation and inflammation in HIV-infected persons, contributing to atherosclerosis development via HIV-mediated endothelial injury and the promotion of a pro-thrombotic state.[22] Larger studies from high-income settings have also found that CVD in PLHIV is associated with abacavir and protease inhibitor use.[16,17,19] Results regarding the CVD risk of abacavir have been particularly controversial.[20,23-29] However, given the very low rate of abacavir use in Brazil, our results do not substantially influence this debate. Protease inhibitor use, although not significant in our multivariate model, was associated with a small increase in the risk of CVD which is consistent with earlier work.[16]

Short-term and long-term survival after myocardial infarction or stroke has improved substantially over the past 20 years in high-income countries, most likely due to improvements in revascularization, effective acute treatment and long-term secondary prevention.[30,31] Nevertheless, current evidence indicates that CVD survivors remain at a two-fold higher risk of all-cause mortality for up to ten years after their event when compared with age-matched members of the general population.[10-12] Our findings for PLHIV in Brazil are consistent with this data, suggesting the added risk of mortality after a CVD event is not influenced by HIV.

Supporting this notion, a French study evaluating one-year mortality rates in myocardial infarction survivors found no difference between patients with and without HIV.[13] Although there is evidence among the English general population that increased mortality associated with past CVD is strongly influenced by age and gender,[11] the low number of patients with a history of CVD in our analysis precluded us from investigating such differences.

This multisite study draws from a diverse clinical population in Brazil. The comprehensive data collected was strengthened by standardized validation of CVD. Our study also leveraged the Brazilian national systems of HIV laboratory data and death registry. Nevertheless, there were some important limitations. Firstly, the low number of CVD events meant our analysis was underpowered to detect a significant effect of some well-known CVD risk factors, for example, sex and CD4 cell count. We also had limited data on some important variables including fatal myocardial infarction and fatal stroke, time-updated smoking status, and validated low-grade dyslipidemia.

This study emphasizes the importance of managing both traditional and HIV-specific factors to reduce CVD risk among ART users in Brazil. We have also demonstrated that PLHIV with a history of CVD have a high risk of death on ART. CVD care and treatment remain priorities for PLHIV in Brazil as this population ages and ART use expands.

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Legends

Table 1. Baseline characteristics*.

*Baseline for CVD analysis was the date of ART initiation while baseline for the mortality analysis was six months after ART initiation or the date of first CVD event, whichever came last (six months after ART initiation was defined as baseline for those without documentation of a CVD event); All values are n (%total) unless otherwise indicated; CVD, cardiovascular disease; IQR, interquartile range; ART, antiretroviral therapy; CRT, São Paulo State Department of Health STD/AIDS Referral and Training Center; HUPES, Professor Edgard Santos University Hospital; INI, National Institute of Infectology Evandro Chagas - Fiocruz; UFMG, Federal University of Minas Gerais

Figure 1. Probability of cardiovascular disease by sex and age.

CVD, cardiovascular disease; yo, years old

Table 2. Factors associated with cardiovascular disease

*Diabetes was strongly correlated with high-grade dyslipidemia and therefore excluded from the multivariate model; ^Multivariate results generated by substituting nadir CD4 with this variable in the main adjusted model; CI, confidence interval; HR, sub-distribution hazard ratio; CVD, cardiovascular disease; ART, antiretroviral therapy; CRT, São Paulo State Department of Health STD/AIDS Referral and Training Center; HUPES, Professor Edgard Santos University Hospital; INI, National Institute of Infectology Evandro Chagas - Fiocruz; UFMG, Federal University of Minas Gerais

Figure 2. Probability of death on antiretroviral therapy with and without prior cardiovascular disease

CVD, cardiovascular disease

Table 3. Factors associated with all-cause mortality

*Multivariate results generated by substituting current CD4 with this variable in the main adjusted model; CI, confidence interval; HR, sub-distribution hazard ratio; CVD, cardiovascular disease; ART, antiretroviral therapy; CRT, São Paulo State Department of Health STD/AIDS Referral and Training Center; HUPES, Professor Edgard Santos University Hospital; INI, National Institute of Infectology Evandro Chagas - Fiocruz; UFMG, Federal University of Minas Gerais

Table 1 – Baseline characteristics*

Characteristic		CVD analysis (n=5,614)	Mortality analysis (n=5,381)
Age, years	Median (IQR)	36.8 (30.4-44.3)	36.8 (30.3-44.3)
Sex	Male	3,750 (66.8)	3,586 (66.6)
	Female	1,864 (33.2)	1,795 (33.4)
Race	White	3,032 (54.0)	2,916 (54.2)
	Black	972 (17.3)	927 (17.2)
	Mixed black	1,332 (23.7)	1,277 (23.7)
	Other	278 (5.0)	261 (4.9)
HIV exposure	Heterosexual	2,956 (52.7)	2,845 (52.9)
	Men who have sex with men	1,685 (30.0)	1,628 (30.3)
	Intravenous drug use	177 (3.2)	170 (3.2)
	Other	796 (14.2)	738 (13.7)
Past cardiovascular disease	No	5,541 (98.7)	5,232 (97.2)
	Yes	73 (1.3)	149 (2.8)
Hypertension	No	5,130 (91.4)	4,867 (90.5)
	Yes	484 (8.6)	514 (9.6)
High-grade dyslipidemia	No	5,441 (96.9)	5,110 (95.0)
	Yes	173 (3.1)	271 (5.0)
Diabetes	No	5,448 (97.0)	5,192 (96.5)
	Yes	166 (3.0)	189 (3.5)
Smoking status at ART initiation	Never	1,399 (24.9)	1,324 (24.6)
	Ever	2,897 (51.6)	2,803 (52.1)
	Unknown	1,318 (23.5)	1,254 (23.3)
Nadir CD4 at ART initiation, cells/mm^3	Median (IQR)	208 (93-292)	208 (95-292)
	Unknown	207 (3.7)	202 (3.8)
CD4, cells/mm^3	Median (IQR)	234 (116-327)	351 (223-484)
	Unknown	562 (10.0)	707 (13.1)
CD4/CD8 ratio	Median (IQR)	0.24 (0.13-0.39)	0.36 (0.22-0.56)
	Unknown	1,872 (33.4)	1,659 (30.8)
HIV viral load, copies/ml	Median (IQR)	42,590 (7,433-142,968)	0 (0-65)
	Unknown	971 (17.3)	768 (14.3)
AIDS diagnosis prior to ART initiation	No	3,550 (63.2)	3,406 (63.3)
	Yes	2,064 (36.8)	1,975 (36.7)

Abacavir use	No	5,567 (99.2)	5,320 (98.9)
	Yes	47 (0.8)	61 (1.1)
Protease inhibitor use	No	3,974 (70.8)	3,590 (66.7)
	Yes	1,640 (29.2)	1,791 (33.3)
Year of ART initiation	2000-2004	800 (14.3)	783 (14.6)
	2005-2009	2,264 (40.3)	2,191 (40.7)
	2010-2014	2,550 (45.4)	2,407 (44.7)
HIV clinic	CRT	907 (16.2)	867 (16.1)
	HUPES	356 (6.3)	317 (5.9)
	INI	1,939 (34.5)	1,892 (35.2)
	Partenon	1,268 (22.6)	1,200 (22.3)
	Rio Preto	384 (6.8)	376 (7.0)
	Santana	247 (4.4)	236 (4.4)

Table 2 – Factors associated with cardiovascular disease

Characteristic		CVD events	Person years	Rate per 1,000 person years (95%CI)	Univariate		Multivariate	
					HR (95%CI)	p	HR (95%CI)	p
Overall		96	27,328.7	3.5 (2.9-4.3)				
Age, years	<35	7	8,408.6	0.8 (0.4-1.7)	1.0		1.0	
	35-44	24	10,139.1	2.4 (1.6-3.5)	3.2 (1.4-7.3)	0.01	2.4 (1.0-5.5)	0.05
	45-54	35	6,419.0	5.5 (3.9-7.6)	7.8 (3.5-17.4)	<0.01	3.9 (1.6-9.4)	<0.01
	55+	30	2,362.0	12.7 (8.9-18.2)	18.1 (8.0-41.1)	<0.01	6.4 (2.5-16.3)	<0.01
Sex	Female	31	9,570.7	3.2 (2.3-4.6)	1.0		1.0	
	Male	65	17,758.0	3.7 (2.9-4.7)	1.1 (0.7-1.7)	0.67	1.4 (0.8-2.3)	0.20
Race	White	48	15,520.4	3.1 (2.3-4.1)	1.0		1.0	
	Black	20	4,511.0	4.4 (2.9-6.9)	1.4 (0.8-2.3)	0.23	1.8 (1.0-3.1)	0.04
	Mixed black	26	6,080.4	4.3 (2.9-6.3)	1.3 (0.8-2.1)	0.24	1.5 (0.9-2.6)	0.12
	Other	2	1,217.0	1.6 (0.4-6.6)	0.5 (0.1-2.1)	0.37	0.5 (0.1-2.1)	0.34
HIV exposure	Heterosexual	60	15,253.9	3.9 (3.1-5.1)	1.0		1.0	
	Men who have sex with men	23	8,117.7	2.8 (1.9-4.3)	0.7 (0.4-1.2)	0.18	1.0 (0.6-1.9)	0.89
	Intravenous drug use	2	974.3	2.1 (0.5-8.2)	0.5 (0.1-2.0)	0.33	0.8 (0.2-3.6)	0.82
	Other	11	2,982.9	3.7 (2.0-6.7)	0.8 (0.4-1.5)	0.50	1.0 (0.5-2.0)	0.92
Past CVD event	No	82	27,019.6	3.0 (2.4-3.8)	1.0		1.0	
	Yes	14	309.2	45.3 (26.8-76.5)	14.3 (8.0-25.8)	<0.01	3.0 (1.4-6.2)	<0.01
Current hypertension	No	56	24,084.1	2.3 (1.8-3.0)	1.0		1.0	
	Yes	40	3,244.6	12.3 (9.0-16.8)	5.6 (3.7-8.5)	<0.01	1.8 (1.0-3.1)	0.04
Current high-grade dyslipidemia	No	42	24,898.9	1.7 (1.2-2.3)	1.0		1.0	
	Yes	54	2,429.8	22.2 (17.0-29.0)	15.6 (10.2-23.9)	<0.01	9.3 (6.0-14.6)	<0.01

Current diabetes*	No	84	25,880.1	3.2 (2.6-4.0)	1.0			
	Yes	12	1,448.6	8.3 (4.7-14.6)	2.6 (1.4-4.9)	<0.01	-	
Smoking status at ART initiation	Never	10	6,390.2	1.6 (0.8-2.9)	1.0		1.0	
	Ever	75	14,439.7	5.2 (4.1-6.5)	3.3 (1.7-6.4)	<0.01	2.4 (1.2-5.0)	0.02
	Unknown	11	6,498.9	1.7 (0.9-3.1)	-		-	
Nadir CD4 at ART initiation, cells/mm^3	>250	20	8,375.8	2.4 (1.5-3.7)	1.0		1.0	
	100-250	38	10,319.0	3.7 (2.7-5.1)	1.6 (0.9-2.8)	0.08	1.8 (1.0-3.2)	0.05
	<100	27	7,369.9	3.7 (2.5-5.3)	1.6 (0.9-2.8)	0.12	1.5 (0.8-2.9)	0.21
	Unknown	11	1,264.1	8.7 (4.8-15.7)	-		-	
Current CD4^, cells/mm^3	>500	40	12,287.0	3.3 (2.4-4.4)	1.0		1.0	
	350-500	14	6,056.0	2.3 (1.4-3.9)	0.7 (0.4-1.2)	0.17	0.7 (0.3-1.2)	0.20
	200-349	32	5,299.3	6.0 (4.3-8.5)	1.6 (1.0-2.6)	0.08	1.6 (0.9-2.8)	0.11
	<200	8	3,390.4	2.4 (1.2-4.7)	0.5 (0.3-1.1)	0.10	0.6 (0.3-1.3)	0.23
	Unknown	2	296.0	6.8 (1.7-27.0)	-		-	
Current CD4/CD8 ratio^	>0.7	23	7,262.9	3.2 (2.1-4.8)	1.0		1.0	
	0.4-0.7	20	8,138.3	2.5 (1.6-3.8)	0.7 (0.4-1.4)	0.33	0.8 (0.4-1.4)	0.38
	<0.4	40	9,260.5	4.3 (3.2-5.9)	1.2 (0.7-2.0)	0.56	1.3 (0.8-2.4)	0.32
	Unknown	13	2,667.1	4.9 (2.8-8.4)	-		-	
Current HIV viral load	Undetectable	82	22,003.2	3.7 (3.0-4.6)	1.0		1.0	
	Detectable	12	4,893.2	2.5 (1.4-4.3)	0.5 (0.3-1.0)	0.04	0.7 (0.4-1.4)	0.29
	Unknown	2	432.3	4.6 (1.2-18.5)	-		-	
AIDS diagnosis prior to ART initiation	No	58	16,964.1	3.4 (2.6-4.4)	1.0		1.0	
	Yes	38	10,364.6	3.7 (2.7-5.0)	1.1 (0.7-1.6)	0.73	0.8 (0.5-1.2)	0.22
Current abacavir use	No	94	26,891.1	3.5 (2.9-4.3)	1.0		1.0	

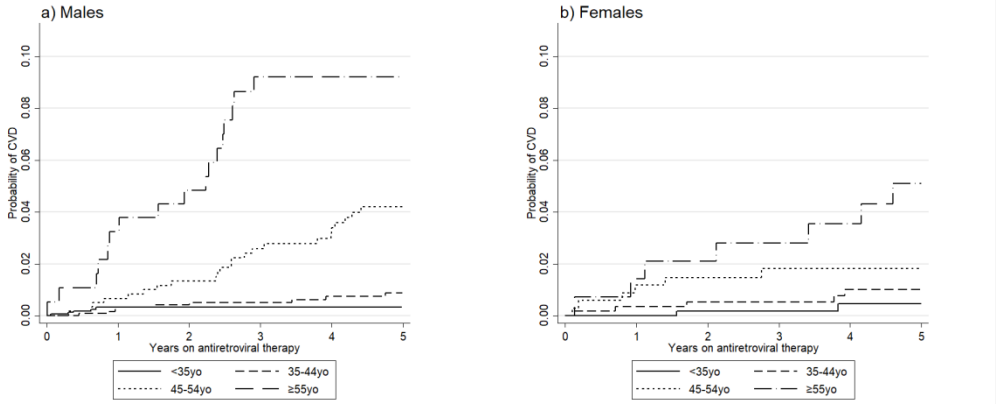
	Yes	2	437.6	4.6 (1.1-18.3)	1.2 (0.3-4.9)	0.79	0.8 (0.2-3.3)	0.78
Current protease inhibitor use	No	54	16,067.0	3.4 (2.6-4.4)	1.0		1.0	
	Yes	42	11,261.7	3.7 (2.8-5.0)	1.2 (0.8-1.7)	0.49	1.1 (0.7-1.8)	0.53
Year of ART initiation	2000-2004	21	6,696.9	3.1 (2.0-4.8)	1.0		1.0	
	2005-2009	58	13,609.5	4.3 (3.3-5.5)	1.2 (0.7-1.9)	0.50	1.1 (0.6-2.1)	0.85
	2010-2014	17	7,022.3	2.4 (1.5-3.9)	0.6 (0.3-1.1)	0.07	0.5 (0.2-1.0)	0.06
HIV clinic	CRT	11	4,579.0	2.4 (1.3-4.3)	1.0		1.0	
	HUPES	3	1,012.8	3.0 (1.0-9.2)	1.2 (0.3-4.1)	0.82	0.8 (0.2-3.3)	0.72
	INI	48	10,235.3	4.7 (3.5-6.2)	2.0 (1.1-3.8)	0.04	0.8 (0.4-1.8)	0.66
	Partenon	17	5,693.0	3.0 (1.9-4.8)	1.3 (0.6-2.7)	0.55	1.2 (0.5-2.8)	0.62
	Rio Preto	6	2,203.4	2.7 (1.2-6.1)	1.2 (0.4-3.2)	0.73	1.2 (0.4-3.3)	0.74
	Santana	3	1,098.9	2.7 (0.9-8.5)	1.2 (0.3-4.4)	0.75	1.0 (0.3-3.8)	0.99

Table 3 – Factors associated with all-cause mortality

Characteristic		Deaths	Person years	Rate per 1,000 person years (95%CI)	Univariate		Multivariate	
					HR (95%CI)	p	HR (95%CI)	p
Overall		418	25,110.7	16.6 (15.1-18.3)				
Age, years	<35	91	7,321.7	12.4 (10.1-15.3)	1.0		1.0	
	35-44	146	9,401.0	15.5 (13.2-18.3)	1.2 (1.0-1.6)	0.11	1.2 (0.9-1.6)	0.16
	45-54	116	6,067.7	19.1 (15.9-22.9)	1.5 (1.1-2.0)	<0.01	1.5 (1.1-2.0)	0.01
	55+	65	2,320.4	28.0 (22.0-35.7)	2.2 (1.6-3.0)	<0.01	2.0 (1.4-3.0)	<0.01
Sex	Female	139	8,907.6	15.6 (13.2-18.4)	1.0		1.0	
	Male	279	16,203.1	17.2 (15.3-19.4)	1.1 (0.9-1.3)	0.36	1.3 (1.0-1.6)	0.05
Race	White	209	14,275.6	14.6 (12.8-16.8)	1.0		1.0	
	Black	89	4,185.5	21.3 (17.3-26.2)	1.5 (1.1-1.9)	<0.01	1.3 (1.0-1.7)	0.07
	Mixed black	103	5,516.2	18.7 (15.4-22.6)	1.3 (1.0-1.6)	0.03	1.3 (1.0-1.7)	0.02
	Other	17	1,133.5	15.0 (9.3-24.1)	1.1 (0.6-1.7)	0.84	0.9 (0.5-1.5)	0.61
HIV exposure	Heterosexual	254	14,124.6	18.0 (15.9-20.3)	1.0		1.0	
	Men who have sex with men	81	7,396.5	11.0 (8.8-13.6)	0.6 (0.5-0.8)	<0.01	0.8 (0.6-1.1)	0.20
	Intravenous drug use	40	924.1	43.3 (31.8-59.0)	2.4 (1.7-3.3)	<0.01	1.7 (1.2-2.5)	<0.01
	Other	43	2,665.5	16.1 (12.0-21.8)	0.8 (0.6-1.1)	0.16	1.0 (0.7-1.4)	0.92
Past CVD event	No	391	24,474.1	16.0 (14.5-17.6)	1.0		1.0	
	Yes	27	636.6	42.4 (29.1-61.8)	2.6 (1.7-3.9)	<0.01	1.7 (1.1-2.7)	0.01
Current hypertension	No	350	22,007.4	15.9 (14.3-17.7)	1.0		1.0	
	Yes	68	3,103.3	21.9 (17.3-27.8)	1.4 (1.0-1.8)	0.02	1.0 (0.8-1.4)	0.78
Current high-grade dyslipidemia	No	356	22,632.8	15.7 (14.2-17.5)	1.0		1.0	
	Yes	62	2,478.0	25.0 (19.5-32.1)	1.5 (1.2-2.0)	<0.01	1.2 (0.9-1.7)	0.22

Current diabetes	No	373	23,683.0	15.7 (14.2-17.4)	1.0		1.0	
	Yes	45	1,427.8	31.5 (23.5-42.2)	2.0 (1.4-2.7)	<0.01	1.6 (1.1-2.2)	0.02
Smoking status at ART initiation	Never	75	5,832.9	12.9 (10.3-16.1)	1.0		1.0	
	Ever	256	13,276.5	19.3 (17.1-21.8)	1.5 (1.2-1.9)	<0.01	1.3 (0.9-1.7)	0.13
	Unknown	87	6,001.3	14.5 (11.7-17.9)	-		-	
Nadir CD4 at ART initiation*, cells/mm^3	>250	100	7,490.8	13.3 (11.0-16.2)	1.0		1.0	
	100-250	166	9,583.2	17.3 (14.9-20.2)	1.3 (1.0-1.7)	0.04	1.1 (0.9-1.4)	0.45
	<100	123	6,840.2	18.0 (15.1-21.5)	1.4 (1.0-1.8)	0.03	1.1 (0.8-1.5)	0.43
	Unknown	29	1,196.6	24.2 (16.8-34.9)	-		-	
Current CD4, cells/mm^3	>500	75	12,113.0	6.2 (4.9-7.8)	1.0		1.0	
	350-500	58	5,580.7	10.4 (8.0-13.4)	1.9 (1.3-2.6)	<0.01	1.6 (1.1-2.3)	0.01
	200-349	100	4,357.7	22.9 (18.9-27.9)	4.3 (3.1-5.8)	<0.01	3.1 (2.3-4.3)	<0.01
	<200	171	2,527.8	67.6 (58.2-78.6)	12.3 (9.3-16.2)	<0.01	7.7 (5.6-10.6)	<0.01
	Unknown	14	531.5	26.3 (15.6-44.5)	-		-	
Current CD4/CD8 ratio*	>0.7	57	7,189.6	7.9 (6.1-10.3)	1.0		1.0	
	0.4-0.7	74	7,680.5	9.6 (7.7-12.1)	1.3 (0.9-1.8)	0.16	1.1 (0.8-1.5)	0.70
	<0.4	238	7,613.9	31.3 (27.5-35.5)	4.4 (3.3-6.0)	<0.01	2.5 (1.8-3.4)	<0.01
	Unknown	49	2,626.8	18.7 (14.1-24.7)	-		-	
Current HIV viral load	Undetectable	230	21,072.4	10.9 (9.6-12.4)	1.0		1.0	
	Detectable	172	3,482.5	49.4 (42.5-57.4)	4.6 (3.7-5.5)	<0.01	2.1 (1.7-2.7)	<0.01
	Unknown	16	555.9	28.8 (17.6-47.0)	-		-	
AIDS diagnosis prior to ART initiation	No	236	15,554.5	15.2 (13.4-17.2)	1.0		1.0	
	Yes	182	9,556.2	19.0 (16.5-22.0)	1.3 (1.1-1.6)	0.01	1.1 (0.9-1.3)	0.56
Year of ART initiation	2000-2004	112	6,554.9	17.1 (14.2-20.6)	1.0		1.0	

	2005-2009	251	12,721.3	19.7 (17.4-22.3)	1.2 (1.0-1.6)	0.09	1.3 (1.0-1.6)	0.06
	2010-2014	55	5,834.5	9.4 (7.2-12.3)	0.6 (0.4-0.8)	<0.01	0.7 (0.5-1.0)	0.04
HIV clinic	CRT	42	4,151.0	10.1 (7.5-13.7)	1.0		1.0	
	HUPES	12	1,022.8	11.7 (6.7-20.7)	1.3 (0.7-2.5)	0.39	1.2 (0.6-2.4)	0.60
	INI	162	9,394.0	17.2 (14.8-20.1)	1.9 (1.3-2.7)	<0.01	1.6 (1.1-2.3)	0.01
	Partenon	115	5,245.9	21.9 (18.3-26.3)	2.4 (1.7-3.4)	<0.01	1.8 (1.2-2.6)	<0.01
	Rio Preto	52	2,043.8	25.4 (19.4-33.4)	2.7 (1.8-4.1)	<0.01	1.6 (1.0-2.5)	0.03



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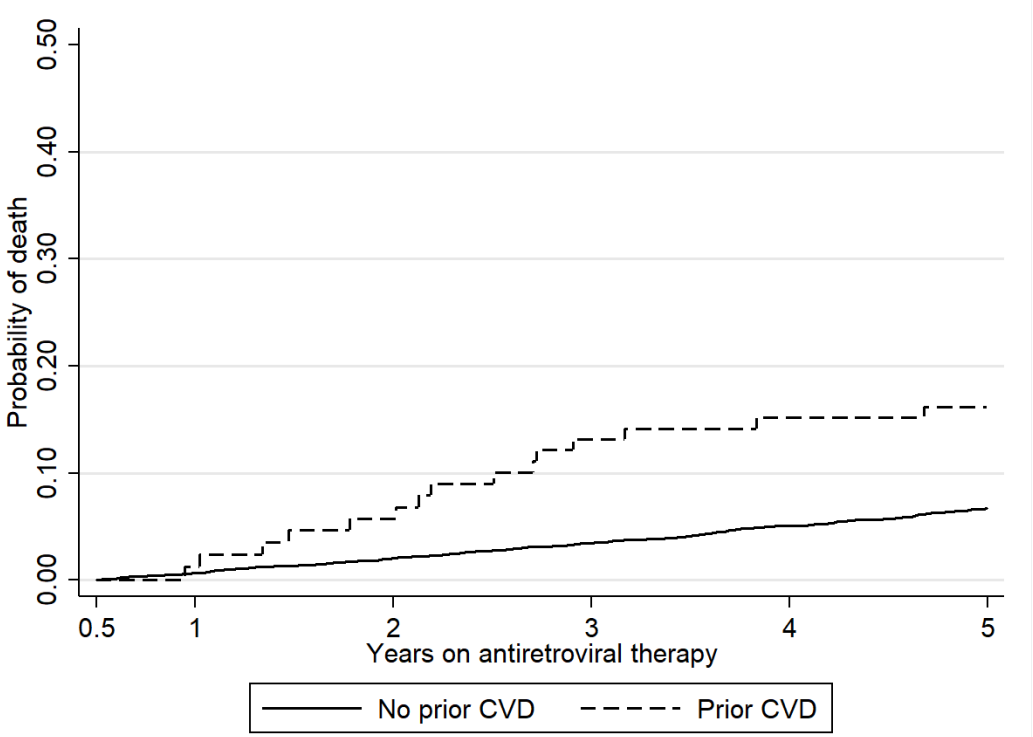

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