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Distribution and performance of cardiovascular risk scores in a mixed population of HIV-infected and community-based HIV-uninfected individuals in Uganda

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Abstract

Background—The utility and validity of CVD risk scores are not well-studied in sub-Saharan Africa. We compared and correlated CVD risk scores with carotid intima media thickness (c-IMT) among HIV-infected and uninfected people in Uganda.

Methods—We first calculated CVD risk using the 1) Framingham laboratory-based score; 2) Framingham non-laboratory score (FRS-BMI); 3) Reynolds risk score; 4) American College of Cardiology and American Heart Association score; and 5) the Data-collection on Adverse Effects of Anti-HIV Drugs score. We then compared absolute risk scores and risk categories across each score using Pearson correlation, and kappa statistics, respectively. Finally, we fit linear regression models to estimate the strength of association between each risk score and c-IMT.

Results—Of 205 participants, half were female and median age was 49 years (IQR 46, 53). Median CD4 count was 430 cells/mm^3 (IQR 334, 546), with median 7 years of ART exposure

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(IQR 6.4, 7.5). HIV-uninfected participants had a higher median systolic blood pressure (121 mmHg vs. 110 mmHg), prevalent current smoking (18% vs. 4%, p=0.001), higher median CVD risk scores (p<0.003), and greater c-IMT (0.68 vs. 0.63, p=0.003). Overall, FRS-BMI was highly correlated with other risk scores (all rho >0.80). In linear regression models, we found significant correlations between increasing CVD risk and higher c-IMT (p<0.01 in all models).

Conclusions—In this cross-sectional study from Uganda, the FRS-BMI correlated well with standard risk scores and c-IMT. HIV-uninfected individuals had higher risk scores than HIV-infected individuals, and the difference appeared to be driven by modifiable factors.

Keywords

Cardiovascular disease; Risk estimation; HIV/AIDS; Sub-Saharan Africa; Body mass index

Introduction

There is a growing burden of non-communicable diseases (NCDs) in sub-Saharan Africa (SSA).[1] Mortality from NCDs is disproportionately worse in low and middle-income countries (LMIC) compared to high-income countries, and cardiovascular diseases (CVD) account for nearly half of these deaths.[2,3] However, most estimates on global disease risk are populated from data outside the SSA region, where primary data on both cardiovascular disease epidemiology and mortality are limited.[3] An important priority for the region will be to expand the availability of CVD risk factors, outcomes, and mortality data to better define the CVD public health priorities, and identify interventions to promote health that are scalable and sustainable in the local context.[4,5]

CVD risk prediction scores can quantify the burden of CVD at both an individual and population level, and are widely accepted as one of the cornerstones of CVD management.[6,7] Since the initial publication of a multivariate analysis to predict coronary disease risk using the Framingham Cohort approximately 50 years ago, multiple novel CVD risk prediction scores have been developed to address population-specific risk factors.[8] The Framingham lipid based risk score (FRS-Lipids), is the most widely used and it has been updated with a non-laboratory, office-based measurement using body mass index instead of lipids (FRS-BMI) to simplify risk estimation.[9] The Reynolds risk score most notably incorporated high-sensitivity C-reactive protein (hsCRP) and family history of CVD, which are independently associated with increased risk of CVD, but had not been included in prior CVD risk models.[10,11] Recently, the American College of Cardiology and American Heart Association (ACC/AHA) derived a score from several geographic and ethnically diverse cohorts in the United States.[12] Finally, the Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study collaborators developed an HIV specific risk score to account for unique pathophysiology of CVD risk that has been postulated for HIV-infected populations.[13]

Whereas CVD risk scores have the potential to enable risk stratification in resource-limited settings, all of the above risk scores were developed from populations in resource-rich settings. Few studies have assessed CVD risk scores in SSA,[14–17] and the utility and validity of commonly used CVD risk assessment tools in SSA remains unclear. Moreover, recent

data suggest that standard CVD scores might under predict true CVD in HIV-infected populations.[18] The objectives of this analysis were to compare and correlate CVD risk profiles with carotid intima media thickness (c-IMT), a surrogate marker of CVD,[19] among a population of HIV-infected people on antiretroviral therapy (ART) and community based age and gender-matched HIV-uninfected people in Uganda.

Methods

Study design and participants

Data were collected as part of the Ugandan Non-Communicable Diseases and Aging Cohort (UGANDAC, NCT02445079), that has been described in details elsewhere.[20,21] Briefly, UGANDAC is a longitudinal cohort study evaluating the epidemiology of cardiovascular and pulmonary disease among older-aged (age ≥ 40 years) people living with HIV in care in Mbarara, Uganda, and age and sex-matched HIV-uninfected comparators enrolled from a village in the clinic catchment area. At each quarterly study visit, participants complete questionnaires on socio-demographic factors and medical history, undergo anthropomorphic and blood pressure measurements, and phlebotomy for hemoglobin A1c, fasting lipid profile, and hsCRP testing.

c-IMT Measurement

A sonographer trained at the University of Wisconsin c-IMT course performed all carotid ultrasonography using standardized protocols.[22] Ultrasonography was performed with a Sonosite M-Turbo (Sonosite, Bothell, Washington). Images of the common carotid artery were collected from the anterior, lateral, and posterior position for a total of 6 images per participant. Far-wall c-IMT was measured in 1-cm segments directly proximal to the carotid bulb, using semi-automated border-detection software (Sono-Calc, version 5.0; Sonosite). A board-certified cardiologist evaluated all images, and low quality images were discarded from the analysis; with the mean value of all adequate images summarized as the mean c-IMT estimate for each participant.[21]

CVD Risk Prediction Scores

For each study participant, we calculated CVD risk with each of the following scores: Framingham lipids-based score (FRS-Lipids), Framingham BMI-based score (FRS-BMI),[9] Reynolds risk score (RRS),[10,11] American College of Cardiology and American Heart Association score (ACC/AHA),[12] and the Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) score (Supplemental Table 1).[13] Those with a hemoglobin A1c equal to or greater than 6.5%, or self-reported history of diabetes and on medications were classified as having diabetes mellitus for scores that included that criterion. We categorized each individual into low, intermediate and high CVD risk, using standard classifications described with each risk score.

Statistical Analysis

We used descriptive statistics to summarize cohort characteristics, CVD risk scores distributions, and risk categories. We compared differences in risk factors between the HIV-infected and uninfected groups using Wilcoxon-rank sum test for continuous variables and

Chi-squared testing for categorical variables. We then compared the absolute FRS-BMI risk score with other scores using the Pearson correlation, and then estimated Cohen's kappa coefficients to assess the degree of agreement between risk score categories (low, intermediate, or high risk). Finally, to estimate the validity of each risk score, we fit linear regression models using the risk scores as the predictor of interest and c-IMT as a surrogate outcome of CVD. Models were conducted both with the total cohort (except for the HIV-specific risk D:A:D score), and then stratified by HIV-serosatus and sex. A *P*-value <0.05 was taken as the level of statistical significance. Analyses were conducted with Stata version 13 (StataCorp, College Station, Texas, USA).

Ethical Statement

The study was reviewed and approved by the ethics review committees of Mbarara University of Science and Technology, and Partners Healthcare, Boston, USA. Consistent with national guidelines, we also received clearance for the study from the Ugandan National Council of Science and Technology and from the Research Secretariat in the Office of the President.

Results

We enrolled 105 (51%) HIV-infected people and 100 (49%) age-gender matched HIV-uninfected controls (Table 1). There were 54 (51%) and 50 (50%) females in the HIV-infected and controls groups, respectively. The median age was 49 years (interquartile range [IQR] 46, 53). Among the HIV-infected participants, the median nadir CD4+ T-Cell count was 122 cells/mm^3 ([IQR] 80, 175 cells/mm^3), and increased to 430 cells/mm^3 ([IQR] 334, 546 cells/mm^3) at the time of data collection, after a median of 7.0 years of ART exposure ([IQR] 6.4, 7.5 years). HIV-infected participants had a higher median hsCRP compared to HIV-uninfected participants (1.2 mg/L IQR [0.5, 3.5 mg/L] versus 0.6 mg/L IQR [0.2, 1.4 mg/L], p < 0.001). Conversely, HIV-uninfected participants had higher median systolic blood pressure (121 mmhg IQR [111, 135 mmHg] versus 110 mmHg [100, 121 mmHg], p < 0.001), more current smokers (18% versus 4%, p=*0.001*) and higher c-IMT (0.68 [IQR 0.63, 0.75] versus 0.62 [IQR 0.58, 0.71], p=0.003). The median total cholesterol was similar between the two groups (163 mg/dl versus 158 mg/dl, p= 0.55). Among the HIV-uninfected participants, only one reported taking anti-hypertensive medications compared to seven among the HIV-infected participants.

Cardiovascular Disease Risk Categorization

HIV-uninfected individuals generally had higher CVD risk scores (Figure 1). For example, the median FRS-Lipids score among HIV-uninfected participants was 5.3% (IQR 3.2, 9.3), compared to 3.6% (IQR 2.2, 6.2 %) among HIV-infected (p < 0.001). The Pearson correlation coefficients ranged from 0.91–0.97 (p<0.001) for all pairs of risk scores (FRS-BMI vs all other risk scores) except for the D:A:D score and Reynolds risk score which had a lower Pearson correlation with FRS-BMI (*rho*= 0.80 and 0.83, p<0.001 respectively).

The Framingham based risk scores and the ACC/AHA classified the majority of participants as low risk (71, 91% and 63, 80%, respectively), whereas the Reynolds and the D:A:D

scores categorized most individuals in the intermediate or high-risk categories (53, 56% and 72%, respectively). Table 2 summarizes the results of pairwise comparisons in score agreement. The laboratory-based and non-laboratory based Framingham based risk scores had very high agreement (≥90%, appa ≥0.6), but lower agreement was seen between the FRS and ACC/AHA scores (appa = 0.4–0.6). In addition, there was relatively little agreement between either RRS or D:A:D and the other CVD risk calculators (appa ≤0.5).

Cardiovascular Disease Risk correlation with c-IMT

In linear regression models, we found significant correlations between increasing CVD risk and higher c-IMT ($p<0.01$ in all models) (Figure 2 and Supplemental Figure 1). Beta-coefficients and corresponding p-values for each model are shown in Table 3.

Discussion

In this analysis from a cohort of HIV-infected individuals on stable ART, and a community-based, HIV-uninfected comparator group, we found that the non-laboratory based Framingham CVD risk prediction score (FRS-BMI) had high agreement with Framingham laboratory based risk score and that all scores correlated relatively well with c-IMT, a surrogate marker of CVD. Our findings are in keeping with prior data that have demonstrated high agreement between non-laboratory based and laboratory based scores both in resource-rich and resource-limited settings.[14–17,23–25] Others have correlated higher c-IMT values and increasing FRS in a predominantly female HIV-infected population in South Africa, and in another multi-country study that included individuals from South Africa.[26,27] While our findings offer additional support for non-laboratory based CVD risk profiling with use of an established surrogate marker of disease, an important next step will be to collect sufficient data to validate these scores with CVD outcomes. Nonetheless, the non-laboratory based scores appear to offer a low-cost, feasible means of CVD risk profiling in resource-limited settings.

Overall there was good correlation between FRS-BMI and other scores. Agreement by major risk categories was imperfect, and in fact poor by kappa scores for many of the comparisons. Importantly, neither the Reynolds risk score (in HIV-uninfected individuals) nor the newer ACC/AHA score agreed well with other scores and would appear to require further investigation before implementation in this setting. For example, because the Reynolds risk score incorporates markers of inflammation, it may prove to be a more valid predictor of CVD events due to the hypothesized role of inflammation and immune activation as a contributor to risk in HIV infected individuals. ACC/AHA is the only risk calculator that incorporates ethnicity such as African American in the risk calculation. However, the use of race-specific coefficients may not translate in African settings because African Americans may have a different risk background when compared to Africans. Finally, we also found that the HIV-specific D:A:D calculator classified significantly greater numbers of HIV-infected individuals with intermediate and high CVD risk than other scores, although the implications of this difference remain unclear.

Although, the Framingham and the D:A:D risk scores have been applied in various SSA populations, they have demonstrated a wide array of CVD risk profiles, presumably because

study populations have also varied widely. For instance, a study of older age, post-menopausal women in western and southern Africa reported generally higher CVD risk based on the Framingham risk score, when compared to our findings.[28] Conversely, a study of younger HIV-infected participants in southwestern Uganda reported relatively low CVD risk.[29] Differences in HIV specific characteristics and CVD risk profiles at the time of risk estimation may partially explain these differences between our risk estimation with the D:A:D score when compared to other studies of HIV-infected participants in SSA.[30–32]

We found that age and gender-matched, community-based, HIV-uninfected individuals had higher CVD risk scores when compared to HIV-infected individuals receiving ART in rural Uganda. The higher CVD risk scores in our study among HIV-uninfected participants were driven largely by a higher systolic blood pressure and smoking rates. We hypothesize that one potential mechanism of this observation could be the additional access to primary care services granted by routine, scheduled HIV care.[4] In fact, approximately 90% of HIV-infected ever-smoking participants were former smokers, compared to 60% of HIV-uninfected; and among the HIV-uninfected participants who were diagnosed with hypertension, only one reported taking anti-hypertensive medications compared to seven among the HIV-infected participants. HIV infection has been associated with lower risk of hypertension in several studies in the region, irrespective of treatment with anti-hypertensive medications, suggesting there might also be other causative mechanisms.[33–37] Alternatively, survivor bias may also account for the lower CVD risk seen in our study among HIV-infected participants. We limited recruitment of HIV-infected participants to those with at least three years of ART use, so by definition excluded those dying before linkage to care or early after ART initiation.

Many cohort studies in resource-rich settings have demonstrated higher incidence of CVD outcomes among HIV-infected populations compared to HIV-uninfected populations receiving clinical care.[38–41] The increased CVD risk in the setting of HIV infection was recently shown to be similar to the increased CVD risk from diabetes in U.S.,[42] which has been well recognized as major risk factor for CVD.[43] A related, outstanding question is whether standard CVD risk scores appropriately estimate risk for HIV-infected populations in SSA and other parts of the world.[44] In our analysis, the D:A:D score correlated well with c-IMT, but notably predicted much greater proportions of individuals with intermediate or high risk than other scores. Although our understanding of the relationship between CVD and HIV in SSA remains limited,[45] persistent immune activation and inflammation among HIV infection in our cohort has been shown to be associated with greater c-IMT.[20,21] Furthermore, and in contrast to our cohort, a high burden of CVD risk factors such as hypertension and metabolic syndrome has also been reported among HIV-infected individuals in this region.[29,46–49] Therefore, additional work will be needed to help clarify if and how HIV infection contributes to CVD risk in SSA, and to what extent treatment of modifiable risk factors such as hypertension mitigates the enhanced risk of CVD.

Our results should be interpreted in the context of limitations. First, this is a cross sectional study so relationships between CVD risk profiles and atherosclerotic burden cannot be presumed to be causative. Second, we attempted to correlate CVD risk scores with a surrogate marker of CVD,[19] as opposed to future risk of coronary heart disease and stroke,

which the scores were designed to predict. Whereas some studies have not demonstrated c-IMT as a strong surrogate for CVD,[50] most studies in the field have,[19] and it is a useful and feasible measure in resource limited settings where more advanced techniques (e.g. coronary angiography and calcium scoring) are not available. Large, adequately powered, prospective studies or registries that include valid measures of these outcomes will be required to more accurately characterize CVD risk in the region. It is likely to be many years before the infrastructure and data are available to assess true cardiovascular outcomes in this region of the world, and as such preliminary data with surrogate measures are useful to generate hypotheses and advance the field.

In conclusion we report that FRS-BMI, a simple non-invasive CVD risk assessment using BMI in place of laboratory-based lipids data had high agreement with a laboratory-based FRS and correlated well with pre-clinical atherosclerosis among individuals in sub-Saharan Africa. This score might offer a simple and feasible approach to improving CVD risk assessment in resource-limited settings. We also noted lower CVD risk scores and c-IMT among HIV-infected participants, and that this difference appeared largely driven by modifiable risk factors such as lower blood pressure and smoking cessation. Further work will be necessary to reconcile the observed lower CVD-risk in the context of persistent inflammation associated with HIV infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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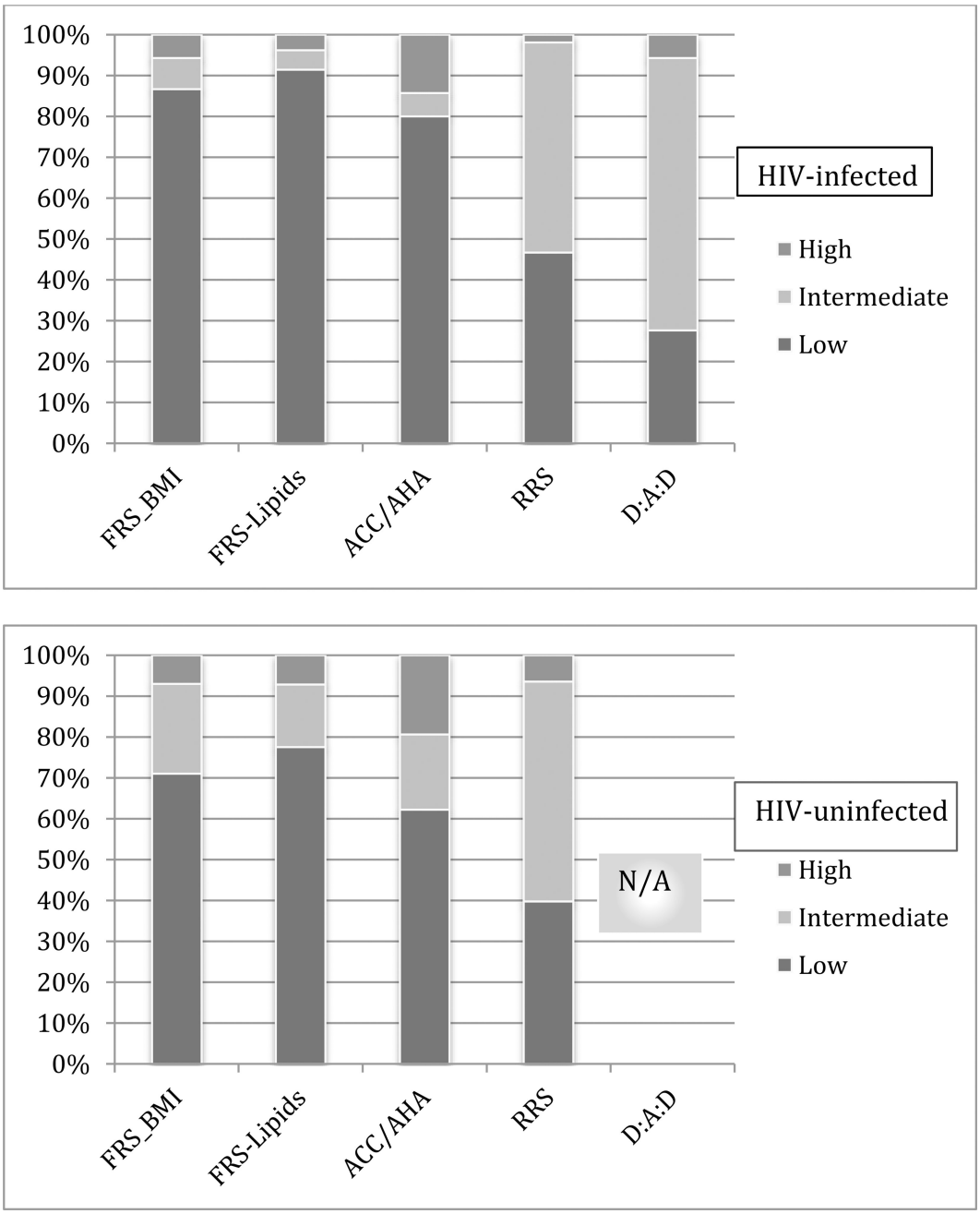

Figure 1.
CVD risk distribution between HIV-infected and HIV-uninfected individuals

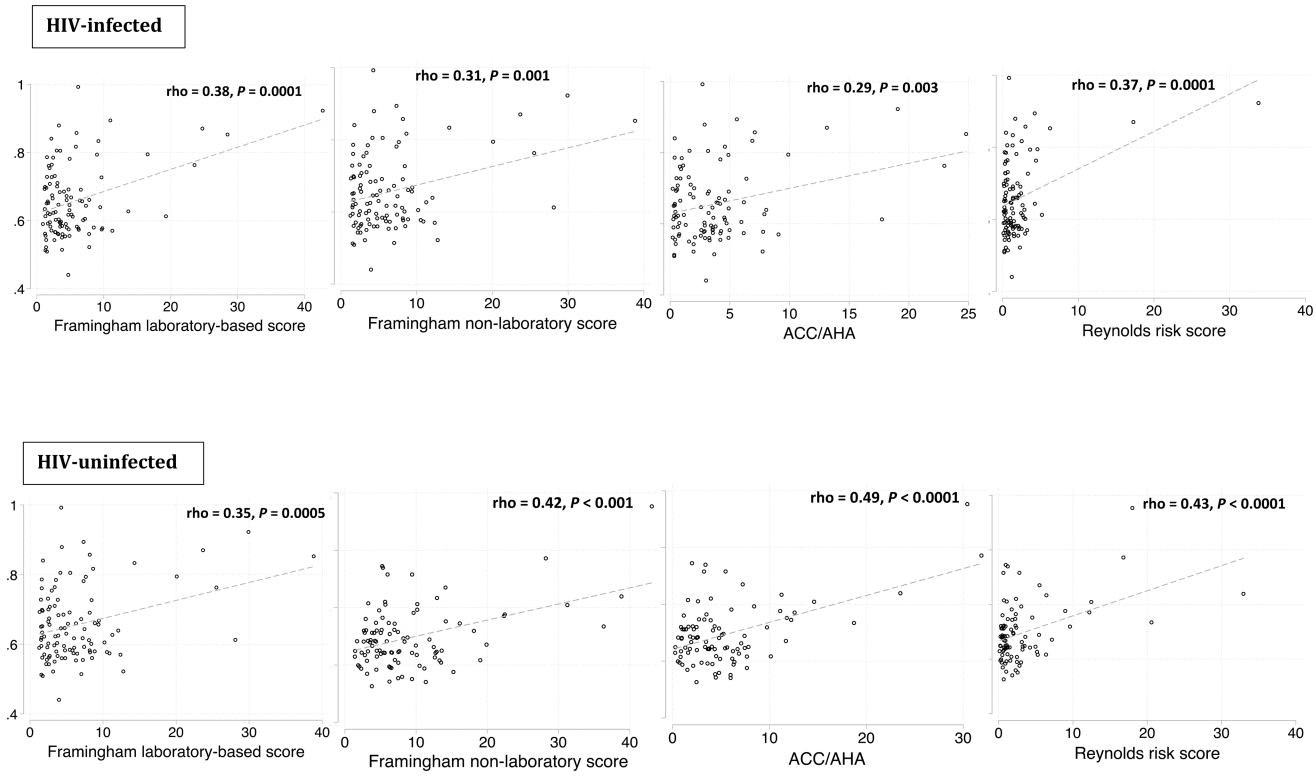

Figure 2.

Scatter plot showing c-IMT by CVD risk. Pearson correlation coefficient and corresponding p-values for each CVD risk factor and c-IMT comparison are shown.

Table 1

Cohort characteristics

Characteristic	HIV-infected	HIV-uninfected	*p*-value[#]
Demographics			
Female sex, n(%)	54 (51)	50 (50)	0.84
Age, yrs median (IQR)	49 (45, 51)	50 (46, 54)	0.05
Cardiovascular Risk Factors			
Overweight or obese, n (%) [*]	28 (27)	23 (23%)	0.54
Current smoker, n(%)	4(3.8)	18 (18)	0.001
Diabetes, n(%) [†]	8 (8)	2 (2)	0.06
Systolic blood pressure, median (IQR)	110 (100, 121)	121 (111, 135)	<0.001
Total cholesterol level (mg/dL), median (IQR)	158 (129, 180)	163 (140, 182)	0.58
HDL cholesterol level (mg/dL), median (IQR)	44 (37, 53)	45 (38, 50)	0.68
hsCRP (mg/L), median (IQR)	1.2 (0.5, 3.5)	0.6 (0.2, 1.4)	<0.001
HIV specific characteristics			
$CD4^+$ nadir (cells/mm^3), median (IQR)	122 (80, 175)	---	---
Current $CD4^+$ (cells/mm^3), median (IQR)	430 (334, 546)	---	---
ART Duration, yrs median (IQR)	7.0 (6.4, 7.5)	---	---
Preclinical Atherosclerosis			
c-IMT, median (IQR)	0.62 (0.58, 0.71)	0.68 (0.63, 0.75)	0.003

Abbreviations: hsCRP: high-sensitivity C-reactive protein

[*] BMI ≥ 25 kg/m2

[†] Diabetes: Hemoglobin A1c ≥ 6.5%.

[#] Wilcoxon-rank sum test for continuous variables and Chi-squared testing for categorical variables were used to summarize cohort characteristics between HIV-infected and uninfected groups.

Table 2

Cardiovascular Risk Scores agreement and corresponding Kappa scores (in parentheses)

Risk Score	FRS-BMI	ACC/AHA	RRS	D:A:D
	% agreement (appa)			
HIV infected				
FRS-Lipids	91 (0.6)	85 (0.4)	52 (0.2)	35 (0.1)
FRS-BMI	---	87 (0.6)	53 (0.2)	37 (0.1)
ACC/AHA	---	---	60 (0.3)	39 (0.2)
RRS	---	---	---	75 (0.6)
HIV uninfected				
FRS-Lipids	90 (0.8)	77 (0.5)	57 (0.3)	---
FRS-BMI	---	81 (0.6)	63 (0.4)	---
ACC/AHA	---	---	65 (0.5)	---

Abbreviations: FRS-Lipids; Framingham laboratory-based score, FRS-BMI; Framingham non-laboratory score, RRS; Reynolds risk score, ACC/AHA; American College of Cardiology and American Heart Association score, D:A:D; Data-collection on Adverse Effects of Anti-HIV Drugs score. Cohen's kappa coefficients were used to assess the degree of agreement between risk score categories (low, intermediate, or high risk).

Table 3

Simple linear regression results evaluating association between CVD risk scores and c-IMT.

	HIV-infected			HIV-uninfected		
Model	**β-coefficient**	**95 % C.I.**	***P***	**β-coefficients**	**95 % C.I.**	***P***
FRS-Lipids	0.007	0.003, 0.010	< 0.001	0.005	0.002, 0.008	< 0.001
FRS-BMI	0.005	0.002, 0.008	0.001	0.006	0.003, 0.008	< 0.001
ACC/AHA	0.007	0.002, 0.012	0.003	0.009	0.006, 0.013	< 0.001
RRS	0.010	0.005, 0.015	< 0.001	---	---	---

Abbreviations: FRS-Lipids; Framingham laboratory-based score, FRS-BMI; Framingham non-laboratory score, RRS; Reynolds risk score, ACC/AHA; American College of Cardiology and American Heart Association score, D:A:D; Data-collection on Adverse Effects of Anti-HIV Drugs score