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MAJOR ARTICLE

Coronary artery disease in persons with HIV without detectable viral replication

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INTRODUCTION: We aimed to determine the prevalence of coronary artery disease (CAD) in persons with HIV (PWH) and investigate if inflammatory markers including interleukin (IL)-6, IL-1β, and high sensitivity C-reactive protein (hsCRP) were associated with CAD.

METHODS: From the Copenhagen Comorbidity in HIV Infection (COCOMO) study, we included virologically suppressed PWH with a coronary CT angiography. Any atherosclerosis was defined as >0% stenosis and obstructive CAD was defined as ≥50% stenosis.

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RESULTS: Among 669 participants (mean age 51 (±11) years, 89% men), 300 (45%) had atherosclerosis, and obstructive CAD was present in 119 (18%). Risk factors including age, male sex, hypertension, diabetes, smoking, dyslipidemia, time with HIV, and current protease inhibitor use were associated with any atherosclerosis and with obstructive CAD. IL-6 and hsCRP>2mg/L were associated with any atherosclerosis and with obstructive CAD in univariable analyses, but not after adjusting for traditional risk factors. IL-1β was not associated with CAD.

CONCLUSIONS: In a large population of PWH without viral replication, almost half had angiography-verified atherosclerosis. High concentrations of IL-6 and hsCRP were univariably associated with CAD but adjusting for cardiovascular risk factors attenuated the association suggesting that inflammation may mediate the association between traditional risk factors and CAD.

KEYWORDS: HIV; CCTA; Undetectable; Comorbidity; Coronary Artery Disease; Inflammation;

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INTRODUCTION

The clinical presentation of cardiovascular disease (CVD) in persons with HIV (PWH) has changed over the last three decades [1]. Since the introduction of antiretroviral therapy (ART), myocarditis and cardiomyopathy has become increasingly rare, and the most common CVDs in PWH are now chronic conditions including heart failure and coronary artery disease (CAD) [1]. The mechanisms leading to CAD in PWH are multifactorial and may include traditional risk factors, ART-associated lipid-perturbation, and HIV-associated immune activation and inflammation [2,3]. Inflammation is lower in well-treated than in untreated PWH, but even in virologically suppressed PWH, markers of systemic inflammation remain elevated compared to uninfected persons, and increased arterial inflammation may be considered a feature of treated HIV infection [4–6]. Evidence for the role of inflammation in the initiation and progression of atherosclerosis has been substantiated by several studies, and the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) unequivocally demonstrated the role of interleukin-1β (IL-1β) in atherogenesis [7]. In PWH, IL-1β has been associated with first-time myocardial infarction and pulmonary disease, and monoclonal antibodies against IL-1β may decrease both circulating markers of inflammation and local arterial inflammation in treated PWH [8–10].

Coronary computed tomography angiography (CCTA) has a high diagnostic accuracy for detection of CAD including determination of CAD-severity [11–13]. Previous studies have found that 52 to 78% of middle-aged PWH have evidence of coronary atherosclerosis. However, although the studies were large and well-conducted, some participants in these studies were not using ART and/or were not virologically suppressed [14–17].

Thus, the distribution of CAD among well-treated PWH remains to be described. We aimed to characterize the burden of CAD and explore factors associated with presence and severity of

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CAD by CCTA among well-treated PWH. We hypothesized that higher levels of inflammatory markers including high-sensitivity C-reactive protein (hsCRP), IL-6 and IL-1β would be associated with both presence and extent of CAD.

METHODS

Study population

Participants were recruited from the Copenhagen Co-morbidity in HIV Infection (COCOMO) study (NCT02382822), a non-interventional cohort study aiming to assess the burden and pathogenesis of non-AIDS comorbidities among the PWH[18]. Inclusion criteria were a positive HIV test and age older than 18 years. Between March 2015 and December 2016, 1,099 participants were enrolled in the study, representing more than 40% of the PWH population residing in the Copenhagen area. Participants were offered a CCTA at entry. The only exclusion criteria for CCTA were reduced renal function or previous contrast induced anaphylaxis. We included all virologically suppressed PWH (defined as HIV-RNA < 50 copies/mL) with a research CCTA. We excluded participants who had CCTA of poor quality.

"Patient consent statement"

All participants provided oral and written informed consent before study inclusion. The COCOMO study (H-8-2014-0004) has been approved by the Ethics Committee of the Capital Region and the Danish Data Protection Agency.

Multi detector computed tomographic angiography image acquisition

All CCTAs were performed using a 320-detector CT scanner (Aquillion One, Canon Medical Systems, Ōtawara, Japan.) using the same scanning protocol. A cardioselective β1-blocker (Metoprolol 25-150 mg) was administered orally approximately 1 hour prior to the procedure if heart rate was above 55 beats per minute unless contraindicated. Participants with inhaler-treated asthma or chronic obstructive pulmonary disease received ivabradin (Corlentor 15 mg, Servier, Copenhagen, Denmark). Prior to image acquisition, one dose of oral spray glyceryltrinitrat (Nitrolingual 0.4 mg Pohl Bos-kamp, Hohenlockstedt, Germany) was administered. An automatic raw data motion analysis tool (PhaseXact, Toshiba) was used to determine the optimal motion free diastolic phase for reconstruction. Images were reconstructed with 0.5-mm slice thickness and increments of 0.25 mm.

Coronary computed tomography angiography analysis

Coronary artery stenosis on CCTA scans were analyzed using the Society of Cardiovascular Computed Tomography coronary segment model [13]. Reviewers were blinded to clinical characteristics. Dedicated software, Vitrea 6.7 (Vital Images, Minneapolis, MN, U.S.A.) was used to perform the analyses. According to clinical practice and the Coronary Artery Disease -

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Reporting and Data System (CAD-RADS) (Figure 1)[13], participants were categorized according to the most severe coronary artery lesion identified : **CAD-RADS 0**, no atherosclerosis: 0% maximal coronary stenosis and no atherosclerosis, **CAD-RADS 1** minimal: 1-24% maximal coronary stenosis or atherosclerosis with no stenosis (only positive remodeling), **CAD-RADS 2**, mild stenosis: 25-49% maximal coronary stenosis, **CAD-RADS 3**, moderate stenosis: 50-69% maximal coronary stenosis, **CAD-RADS 4a**, severe stenosis: 70-99% maximal coronary stenosis, **CAD-RADS 4b**, severe stenosis: >50% LM stenosis or three-vessel obstructive (≥70% stenosis) disease, **CAD-RADS 5**, total occlusions: 100% maximal coronary stenosis. **CAD-RADS Nondiagnostic,** >50% coronary artery disease cannot be excluded in patient without obstructive disease in remaining segments: If ≥ 1 coronary segment was nondiagnostic due to poor image quality (motion artifacts, poor contrast enhancement, image noise or streak artifacts) the scan was deemed nondiagnostic and excluded from the analyses. "For statistical analyses, the CAD-RADS groups were further categorized into three levels: Any atherosclerosis was defined as CAD-RADS ≥ 1 and obstructive CAD was defined as CAD-RADS ≥ 3 or previous coronary angioplasty or CABG."

Biochemistry and inflammatory markers variables

hsCRP, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, triglycerides, total cholesterol, and plasma glucose were analyzed at a single laboratory at the Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital. hsCRP was analyzed with a high-sensitivity assay using latex-enhanced turbidimetry (Dako, Glostrup, Denmark) or nephelometry (Dade Behring, Deerfield, IL, US). For analyses of inflammatory markers, plasma samples were collected at baseline and stored at −80°C until use. IL-1β was analyzed by an enzyme immunoassay with the Meso Scale (Rockville, MD, US) V-Plex Human IL-1β kit and IL-6 using the magnetic multiplex assay kits from R&D systems. All analyses were done according to the manufacturer's instructions. Absorption was read at 450 nm with wavelength correction set to 540 nm, using a Synergy H1 plate reader (BioTek, Winooski, VT).

Variable definitions

As outcome variable, we grouped participants into three categories based on their CAD-RADS category: No atherosclerosis: CAD-RADS 0; Any atherosclerosis: CAD-RADS ≥ 1; Obstructive atherosclerosis: CAD-RADS ≥ 3 or previous coronary angioplasty or CABG. Age was defined as age as time of CT-scan. We categorized body mass index (BMI) groups according to WHO definitions [19]. Smoking was categorized as never, former, or current smoking. According to guidelines, hypertension was defined as anti-hypertensive treatment and/or as having ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic blood pressure values [20]. Dyslipidemia was defined as low-density lipoprotein (LDL) ≥ 4.16 mmol/L (160 mg/dl) and/or lipid lowering treatment (statins) [21]. Framingham Risk Score for cardiovascular disease (10-year risk) was calculated for participants younger than 75 and participants with score of 10% were categorized as low risk, risk 10-20% was categorized as intermediate risk, and a risk of 20% or more was

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categorized as high risk. High level of inflammatory variables was defined as > 75th percentile for each marker, respectively, and for hsCRP, as >2mg/L. CD4 nadir was defined as lowest recorded CD4 count; previous AIDS was defined as previous AIDS-defining disease; time since HIV diagnosis was defined as time since HIV diagnosis and CT-scan, and use of protease inhibitors was defined as use of drug with the suffix "-navir".

Statistics

Normally distributed continuous variables were reported as mean and standard deviation (SD), whereas non-normally distributed continuous variables were reported as median and interquartile range (IQR). Categorical variables were reported as frequencies with percentages.

Groups were compared using t-test for normally distributed and Mann Whitney U test for non-normally distributed continuous data. For categorical data, χ^2 tests were used. Simple and multiple logistic regression models with a prespecified model including age (per ten-year increase), sex, hypertension, diabetes, and smoking status, were used to analyze the associations of covariates with any atherosclerosis and/or obstructive CAD.

For inflammatory markers, a simple model including age and sex was used. Associations were expressed as crude and adjusted odds ratios (OR) with 95% confidence intervals (CI). Model fit and assumptions of normality for parametric tests were evaluated graphically. All tests were two-sided with an α of 5%.

RESULTS

Of the 1,099 persons with HIV who were included in COCOMO, coronary CT angiography was performed in 724 of whom 686 were virologically suppressed (HIV-RNA <50 copies/mL). We excluded 17 participants due to poor CCTA image quality leaving 669 who were included.

Among the 669 included, the mean age was 51 (standard deviation, SD: 11) years, and 596 (89%) were men. The transmission mode was primarily men having sex with men (76%) or heterosexual transmission (18%). Few (2%) reported ever use of intravenous drug at time of CT scan, 664 (99%) were using cART, and the mean (SD) current CD4 count was 721 (277) cells/μL. The mean (SD) time since HIV diagnosis was 14 (9) years, mean nadir CD4 count was 259 (186) cells/μL, and 270 (40%) PWH had a nadir CD4 count <200 cells/μL. The median concentrations of IL-6IL-1β are listed in Table 1 and stratified by CAD-RADS category in Supplementary table 1.

Coronary artery disease according to severity of disease

Of the 669 included PWH, 300 (45%) had evidence of atherosclerosis, and 84 (13%) and 97 (14%), respectively, had minimal and mild (non-obstructive) atherosclerosis. Obstructive CAD was present in 119 (18%) participants of whom 53 (44%) had moderate stenosis, 30 (25%) had

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severe stenosis, 12 (10%) had one or more occluded coronary artery segments, and 24 (20 %) had previous coronary angioplasty or CABG (Figure 2A). Of the included PWH, 65 (10%) were CAD-RADS nondiagnostic (Supplementary table 2 presents demographic characteristics of non-diagnostic cases). The median number of coronary segments with atherosclerosis was 3 (range 1 to 14 segments, interquartile range: 2 to 5 segments). Figure 2B depicts the number of segments with atherosclerosis among participants who have atherosclerosis corresponding to the segment involvement score[22].

Traditional risk factors and coronary artery disease

Estimates for the univariable and multivariable analyses between potential risk factors and coronary artery disease are presented in Supplementary table 3 and Table 2, respectively. In univariable analyses, traditional risk factors for CAD including age, male sex, hypertension, diabetes, smoking, and dyslipidemia were all associated with both any atherosclerosis and with obstructive CAD.

In multivariable analyses adjusted for our prespecified model (age, sex, smoking status, diabetes, and hypertension), any atherosclerosis, was associated with older age, male sex, hypertension, current smoking, dyslipidemia, and BMI > 30kg/m^2. Obstructive CAD was associated with older age, hypertension, diabetes, current smoking, and dyslipidemia.

Framingham Risk Scores and coronary artery disease

Figure 3 depicts the distribution of coronary artery disease stratified by Framingham Risk Scores. Compared to PWH with low Framingham risk scores, PWH with intermediate Framingham risk scores had OR 4.16 [2.76, 6.27] of any atherosclerosis and OR 3.92 [2.11, 7.29] of obstructive CAD. Compared to PWH with low Framingham risk scores, PWH with high Framingham risk scores had OR 13.51 [8.12, 22.49] of any atherosclerosis and OR 11.47 [6.34, 20.75] of obstructive CAD.

HIV-related risk factors and coronary artery disease

Of HIV-related variables, CD4 nadir < 200 cells/μL, previous AIDS, time since HIV diagnosis and use of protease inhibitors were associated with any atherosclerosis and with obstructive CAD in univariable analyses. In multivariable analyses, we found that time since HIV diagnosis, and current protease inhibitor use were associated with obstructive CAD (Table 2). Controlling for dyslipidemia did not change the parameter estimates for the association between protease inhibitor use and CAD significantly. In both univariable and multivariable analyses, higher current CD4 count was associated with *lower* odds of any atherosclerosis. No other HIV-related variables were associated with any atherosclerosis or obstructive CAD (Table 2)

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Inflammatory markers and coronary artery disease

In univariable analyses, high concentration of IL-6 and hsCRP > 2mg/L were associated with any atherosclerosis, and high level of IL-6 was also associated with obstructive CAD. IL-1β was not associated with coronary atherosclerosis (Table 3). In multivariable analyses adjusted for age and sex, high level of IL-6 was associated with obstructive CAD (adjusted OR: 1.86 [1.13, 3.08], p=.016) but not with any atherosclerosis. IL-1β and hsCRP were not associated with coronary atherosclerosis (Table 4), and no inflammatory markers were associated with CAD indices in models that included traditional cardiovascular risk factors (presented in Table 2). Associations between inflammatory markers and traditional and HIV-related variables are listed in Supplementary Table 4.

DISCUSSION

Among 669 well-treated PWH, almost half had any atherosclerosis, and 18% had obstructive CAD. Traditional risk factors, current protease inhibitor use, and time since HIV diagnosis were associated with both any atherosclerosis and with obstructive CAD in models adjusted for common comfounders including age. We found that high concentration of IL-6 was associated with obstructive CAD independent of age and sex, but the association was attenuated after adjusting further for cardiovascular risk factors, suggesting that inflammation may mediate the association between traditional risk factors and CAD.

A recent large metanalysis concluded that the risk of CVD events in PWH were twice that of uninfected persons [23]. This observation has sparked an interest into the study of sub- or preclinical CAD among PWH using non-invasive cardiac CT [16,24]. Our prevalence estimates are comparable to data from the Swiss HIV cohort (median age 52 years, 86% men) that reported that 53% of PWH had atherosclerosis and 13% had obstructive disease[16]. In North American PWH of similar age, the prevalence seems to be higher. Thus, the Canadian HIV and Aging Cohort Study (mean age 56y, 92% men) reported that 70% of 155 PWH had atherosclerosis and 20% had obstructive disease, and the Multicenter AIDS Cohort Study (MACS) (mean age 53) reported that 78% of 618 HIV-infected men had atherosclerosis and 17% had obstructive disease[15,17]. The discrepancies could, at least in part, be attributed to a better virological control and lower levels of inflammation and/or differences in CVD risk profiles in the European cohorts. Regardless, our data show that one in five of middle-aged, well-treated PWH have obstructive CAD with potential deleterious impact on both survival and quality of life [25,26].

The pathogenesis of CAD in PWH likely reflects an intricate interplay between both traditional and HIV-related factors that may accelerate the development of atherosclerosis [27]. In line with findings from the Swiss HIV cohort [16], we found that traditional risk factors were associated with the higher odds of both having any atherosclerosis and obstructive CAD. Smoking, dyslipidemia, and hypertension in particular, have been subject of scrutiny as these risk factors

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are both modifiable and prevalent among PWH [28,29]. The fact that current smoking, but not former smoking, was associated with higher odds of CAD, emphasizes the importance of smoking cessation. To identify individuals who might benefit from risk factor modification, the European AIDS Clinical Society guidelines recommend Framingham risk score evaluation in men with HIV older than 40 and women with HIV older than 50 years of age [30]. In the well-treated, mainly Caucasian participants in COCOMO, Framingham risk score was able to classify reasonably well, and obstructive CAD was uncommon among participants with low Framingham score. In contrast, 39% of participants with high Framingham had obstructive CAD and more than four in five had coronary atherosclerosis. This suggests that although Framingham risk scores may underestimate the risk of future cardiovascular events in PWH [31], the tool does identify most individuals with atherosclerosis in a population of PWH without viral replication.

The discrepancy between Framingham Risk Score and actual risk of major CVD events has been attributed to HIV-related factors including immune dysfunction, ART toxicity, and chronic inflammation and immune activation [2,3,27,32]. This may be reflected in the association between CAD and time since HIV diagnosis which may reflect a longer treatment-naïve period and/or prior history of severe immune dysfunction, as prompt initiation of ART for all newly diagnosed patients was only recommended by guidelines after 2015. We found that history of severe immune dysfunction or previous AIDS was associated with CAD only in the univariable analyses and not after adjusting for age and other potential confounders. Current use of protease inhibitors, however, was associated with approximately 50% higher odds of CAD in both univariable and in multivariable analyses. Protease inhibitors, especially first generation, are known to perturb lipid metabolism but recent findings indicate that contemporary protease inhibitors may also be associated with higher risk of CVD, and the risk seems to be independent of dyslipidemia [33–35]. The Swiss HIV cohort similarly investigated this in 403 PWH and found a borderline association with atazanavir but not with protease inhibitors *as a group* [36]. A participant's current ART regimen may, however, reflect management decisions due to failure of historical therapy and the effect estimate could be subject to unmeasured confounding. Future, prospective studies are needed to clarify if protease inhibitor use confers an atherogenic effect.

Both hsCRP and IL-6 were associated with CAD in univariable analyses. Chronic inflammation is an established risk factor for atherosclerosis and unspecific inflammatory markers, including IL-6 and hsCRP, have been associated with CVD in PWH [3]. After adjusting for age and sex, high concentration of IL-6 remained associated with obstructive CAD, but IL-6 was no longer associated with any atherosclerosis, and adjustment for cardiovascular risk factors further attenuated the association, which may imply that inflammation lies on the causal pathway between traditional cardiovascular risk factors and CAD. This differed from findings in the REPRIEVE trial where IL-6 was associated with CAD in multivariable models adjusted for traditional and HIV-related risk factors[37]. IL-1β is an upstream proinflammatory cytokine. Effective inhibition of IL-1β induced inflammation decreases the risk of cardiovascular events in uninfected individuals with prior myocardial infarction [7,38]. In the context of HIV infection, a

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smaller study found that treatment IL-1β antibodies lowered arterial inflammation in PWH over a period of 12 weeks [10]. As HIV-related factors including immune function have been associated with the IL-1β pathway, the IL-1 family could link HIV infection to CVD [39,40]. We did not find concentration of IL-1β to be associated with CAD in well-treated PWH. In contrast, a recent case-control study found activity of the IL-1 family to predict first time myocardial infarction in PWH [9]. The discrepancy might be explained by differences in risk profile. Moreover, infarction likely represents an entity distinct from stable CAD, and active inflammation may play a more prominent role in plaque rupture and acute coronary events than in stable atherosclerosis.

Our study has strengths, including a large, well-characterized cohort where data was collected prospectively, but also some important limitations. Participants in COCOMO live in Copenhagen, Denmark and are primarily men of Scandinavian descent. Thus, results may not be applicable to women and to persons from other ethnic groups in other countries. Moreover, the cross-sectional nature of the analyses precludes conclusions regarding.

CONCLUSION

Almost half of middle-aged, well-treated PWH, had angiography-verified atherosclerosis and just under one in five had obstructive CAD. Traditional cardiovascular risk factors, current protease inhibitor use and time since HIV diagnosis were associated with both any atherosclerosis and with obstructive CAD. High concentrations of IL-6 and hsCRP were univariable associated with CAD but adjusting for cardiovascular risk factors attenuated the association suggesting that inflammation may mediate the association between traditional risk factors and CAD.

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CAPTION/LEGENDS

Table 1 Population characteristics

Variable	N = 669
Age in years, mean (SD)	51 (11)
Men, n (%)	596 (89)

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Former Smoker	240 (36)
Current Smoker	186 (28)
Hypertension	284 (42)
Diabetes	19 (2.8)
Body mass index in kg/m^2, mean (SD)	24.6 (3.4)
Body mass index >30 kg/m^2, n (%)	44 (7)
Dyslipidemia	128 (19)
Low density lipoprotein in mM, mean (SD)	2.8 (1)
Using Statin, n (%)	77 (12)
Framingham Risk Score, median (IQR)	15 (11-20)
Low Risk (<10 %), n (%)	289 (43)
Intermediate Risk (≥10 and <20%), n (%)	172 (26)
High Risk (≥20 %), n (%)	153 (23)
Current CD4 < 500cells/μL, n (%)	142 (21)
CD4 nadir < 200cells/μL, n (%)	270 (40)
Time since HIV diagnosis, years (SD)	14 (9)
Protease Inhibitor use, n (%)	200 (30)
hsCRP, mg/L median (IQR)	1.12 (0.55-2.38)
IL-6, pg/mL median (IQR)	3.23 (2.31-4.31)
IL-1β, pg/mL, median (IQR)	0.18 (0.07-0.30)

Demographic characteristics and level of inflammation in the study population. If percentages in each category do not add to 100%, it is due to missing values for that variable.

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Table 2 Adjusted Odds Ratio of any atherosclerosis, and obstructive CAD

Variable	Any atherosclerosis	Obstructive CAD
Age per decade older	3.38 [2.64, 4.33], p<.001	2.85 [2.19, 3.73], p<.001
Male sex	2.70 [1.64, 5.42], p=.005	1.20 [0.49, 2.92], p=.687
Hypertension	1.57 [1.05, 2.37], p=.030	1.66 [1.01, 2.75], p=.046
Diabetes	2.87 [0.80, 10.38], p=.107	2.90 [1.02, 8.24], p=.045
Former Smoker	1.39 [0.86, 2.23], p=.181	1.95 [0.52, 1.72], p=.860
Current Smoker	1.71 [1.04, 2.82], p=.035	2.30 [1.24, 4.26], p=.008
Dyslipidaemia¬	1.81 [1.05, 3.13], p=.032	2.01 [1.11, 3.67], p=.022
BMI > 30kg/m^2 vs normal BMI	3.37 [1.43, 7.93], p=.005	1.26 [0.48, 3.32], p=.644
Current CD4 < 500cells/µL	0.58 [0.35, 0.97], p=.037	0.93 [0.52, 1.64], p=.796
CD4 nadir < 200cells/µL	1.04 [0.68, 1.58], p=.869	1.53 [0.94, 2.47], p=.086
CD4/CD8 ratio	1.03 [0.67, 1.58], p=.901	1.27 [0.82, 1.99], p=.288
Time since HIV diagnosis (per 5 years)	1.16 [1.02, 1.31], p=.024	1.34 [1.16, 1.55], p<.001
Protease Inhibitor use	1.49 [0.96, 2.31], p=.076	1.73 [1.06, 2.84], p=.028
INSTI use	0.71 [0.46, 1.10], p=.121	0.94 [0.56 1.58], p=.815
High level of IL6	1.02 [0.62, 1.68], p =.936	1.56 [0.90, 2.69], p=.110
High level of IL-1β	0.95 [0.61, 1.50], p =.838	1.01 [0.57, 1.77], p=.981
hsCRP>2mg/L	1.11 [0.66;1.86], p =.702	1.11 [0.66, 1.86], p=.702

Adjusted odds ratios between risk factors and any atherosclerosis and obstructive CAD. Adjusted for a prespecified model including age, sex, hypertension, diabetes, and smoking status. High level of inflammatory marker defined as

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upper quartile for each respective marker. For hsCRP, hsCRP>2 mg/L. **Any atherosclerosis:** ≥1% coronary artery stenosis **Obstructive CAD:** Coronary Artery Disease defined as ≥50% coronary artery stenosis; **BMI**: Body mass index; **hsCRP**: high-sensitivity C-reactive protein; **IL**: Interleukin; **INSTI**: Integrase Strand Transfer Inhibitor; ¬Only among participants without previous coronary intervention (CABG/Stent)

Table 3 Inflammation and crude Odds Ratio of any atherosclerosis, and obstructive CAD

Variable	Any atherosclerosis	Coronary Artery Disease (obstructive atherosclerosis)
High level of IL6	2.57 [1.73, 3.81], p<.001	2.83 [1.82, 4.40], p<.001
High level of IL-1β	0.90 [0.62, 1.29], p=.556	1.01 [0.63, 1.63], p=.956
hsCRP>2 mg/L	1.68 [1.18, 2.39], p=.004	1.45 [0.94, 2.22], p=.091

Crude (unadjusted) association between high level of inflammatory markers and any atherosclerosis or obstructive CAD. **Any atherosclerosis:** ≥1% coronary artery stenosis **Obstructive CAD:** Coronary Artery Disease defined as ≥50% coronary artery stenosis; **hsCRP**: high-sensitivity C-reactive protein; **IL**: Interleukin

Table 4 Inflammation and adjusted Odds Ratio of any atherosclerosis, and obstructive CAD

Variable	Any atherosclerosis	Coronary Artery Disease (obstructive atherosclerosis)
High level of IL6	0.96 [0.57, 1.60], p=.871	1.86 [1.13, 3.08], p=.016
High level of IL-1β	0.85 [0.55, 1.33], p=.482	0.93 [0.55, 1.58], P=.791
hsCRP>2 mg/L	1.37 [0.90, 2.07], p=.144	1.08 [0.66, 1.74], p=.768

Minimally adjusted association between high level of inflammatory markers and any atherosclerosis or obstructive CAD. Adjusted for age and sex. **Any atherosclerosis:** ≥1% coronary artery stenosis **Obstructive CAD:** Coronary Artery Disease defined as ≥50% coronary artery stenosis; **hsCRP**: high-sensitivity C-reactive protein; **IL**: Interleukin

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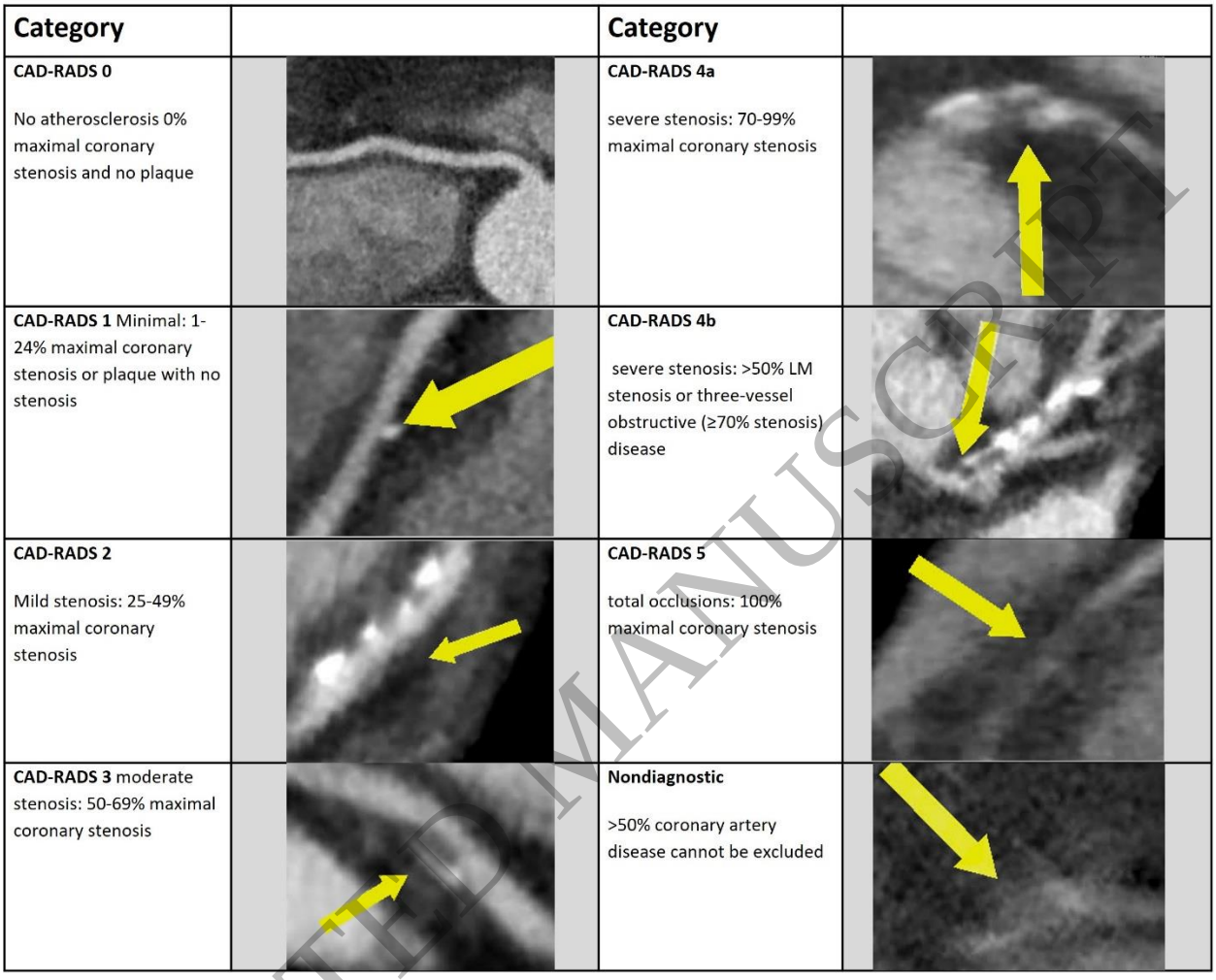
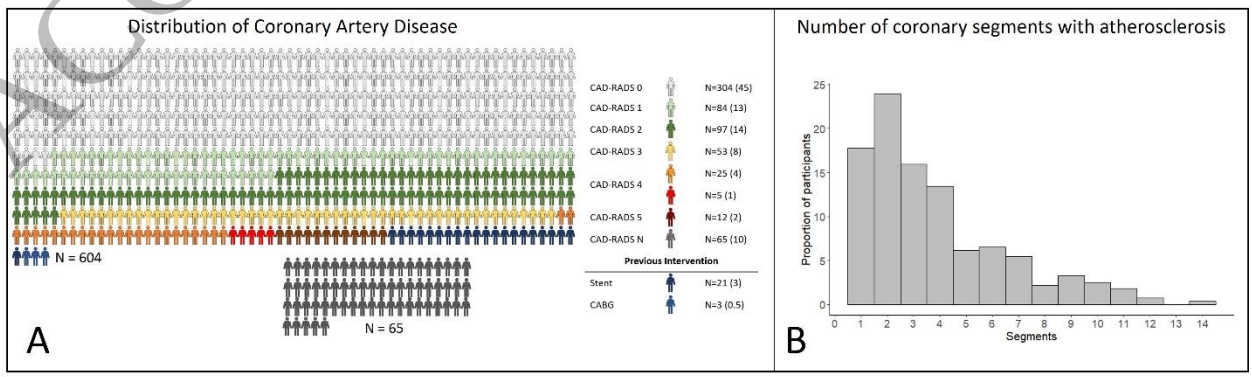
Figure 1 CAD-RADS assessment category definitions with examples



The CAD-RADS category is based on the maximum diameter stenosis in coronary segments with Ø ≥1.5mm. Segments were defined according to the segmental anatomy of the coronary arteries of the Society of Cardiovascular Computed Tomography. **CAD-RADS:** Coronary Artery Disease Reporting and Data System

Figure 2 Distribution of Coronary Artery Disease among well-treated Persons with HIV



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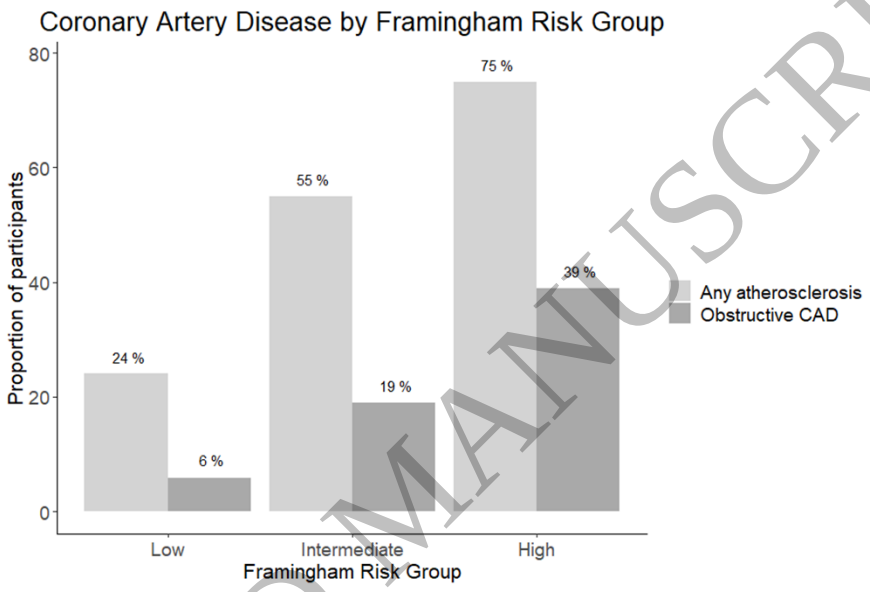
A: The CAD-RADS categories for each of the 669 study participants. **B** Histogram showing the frequency of number of coronary segments with atherosclerosis among participants with atherosclerosis irrespective of stenosis grade (segment involvement score). Segments were defined according to the segmental anatomy of the coronary arteries of the Society of Cardiovascular Computed Tomography. CAD-RADS: Coronary Artery Disease Reporting and Data System

Figure 3 Coronary artery disease by Framingham Risk Group



Coronary artery disease stratified by Framingham Risk Scores. **Any atherosclerosis:** ≥1% coronary artery stenosis **Obstructive CAD:** Coronary Artery Disease defined as ≥50% coronary artery stenosis. **Low Risk: <10%; Intermediate Risk: ≥10% and <20%; High Risk: ≥20%**

REFERENCES

1. Feinstein MJ, Hsue PY, Benjamin LA, et al. Characteristics, Prevention, and Management of Cardiovascular Disease in People Living with HIV: A Scientific Statement from the American Heart Association. Circulation [Internet]. **2019**; :1–27. Available from: https://www.ahajournals.org/doi/10.1161/CIR.0000000000000695
2. Nou E, Lo J, Grinspoon SK. Inflammation, immune activation, and cardiovascular disease in HIV. AIDS. 2016.
3. Duprez DA, Neuhaus J, Kuller LH, et al. Inflammation, Coagulation and Cardiovascular Disease in HIV-Infected Individuals. Thorne C, editor. PLoS One. **2012**; 7(9):e44454.
4. Subramanian S, Tawakol A, Burdo TH, et al. Arterial inflammation in patients with HIV. JAMA - J Am Med Assoc. **2012**; .

ACCEPTED MANUSCRIPT

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5. Knudsen A, Hag AMF, Loft A, et al. HIV infection and arterial inflammation assessed by 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET): A prospective cross-sectional study. J Nucl Cardiol. **2015**; 22(2):372–380.
6. Lawal IO, Ankrah AO, Popoola GO, Lengana T, Sathekge MM. Arterial inflammation in young patients with human immunodeficiency virus infection: A cross-sectional study using F-18 FDG PET/CT. J Nucl Cardiol [Internet]. Springer US; **2019**; :1–8. Available from: https://doi.org/10.1007/s12350-018-1207-x
7. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med. **2017**; :NEJMoa1707914.
8. Thudium RF, Ringheim H, Ronit A, et al. Independent Associations of Tumor Necrosis Factor-Alpha and Interleukin-1 Beta With Radiographic Emphysema in People Living With HIV. Front Immunol [Internet]. Frontiers Media S.A.; **2021**; 12:668113. Available from: https://pubmed.ncbi.nlm.nih.gov/33936110
9. Hoel H, Ueland T, Knudsen A, et al. Soluble Markers of Interleukin 1 Activation as Predictors of First-Time Myocardial Infarction in HIV-Infected Individuals. J Infect Dis. **2020**; .
10. Hsue PY, Li D, Ma Y, et al. IL-1β Inhibition Reduces Atherosclerotic Inflammation in HIV Infection. J. Am. Coll. Cardiol. 2018.
11. Kofoed KF, Kelbæk H, Riis Hansen P, et al. Early versus standard care invasive examination and treatment of patients with non-ST-segment elevation acute coronary syndrome verdict randomized controlled trial. Circulation. **2018**; 138(24):2741–2750.
12. Litt HI, Gatsonis C, Snyder B, et al. CT angiography for safe discharge of patients with possible acute coronary syndromes. N Engl J Med. United States; **2012**; 366(15):1393–1403.
13. Cury RC, Abbara S, Achenbach S, et al. CAD-RADS(TM) Coronary Artery Disease - Reporting and Data System. An expert consensus document of the Society of Cardiovascular Computed Tomography (SCCT), the American College of Radiology (ACR) and the North American Society for Cardiovascular Imaging . J Cardiovasc Comput Tomogr. United States; **2016**; 10(4):269–281.
14. Lai H, Moore R, Celentano DD, et al. HIV Infection Itself May Not Be Associated With Subclinical Coronary Artery Disease Among African Americans Without Cardiovascular Symptoms. J Am Heart Assoc [Internet]. **2016**; 5(3):e002529. Available from: http://jaha.ahajournals.org/lookup/doi/10.1161/JAHA.115.002529
15. Post WS, Budoff M, Kingsley L, et al. Associations between HIV infection and subclinical coronary atherosclerosis. Ann Intern Med. **2014**; 160(7):458–467.
16. Tarr PE, Ledergerber B, Calmy A, et al. Subclinical coronary artery disease in Swiss HIV-positive and HIV-negative persons. Eur Heart J. England; **2018**; 39(23):2147–2154.
17. Boldeanu I, Sadouni M, Mansour S, et al. Prevalence and Characterization of Subclinical Coronary Atherosclerotic Plaque with CT among Individuals with HIV: Results from the Canadian HIV and Aging Cohort Study. Radiology. United States; **2021**; 299(3):571–580.
18. Ronit A, Haissman J, Kirkegaard-Klitbo DM, et al. Copenhagen comorbidity in HIV infection (COCOMO) study: a study protocol for a longitudinal, non-interventional assessment of non-AIDS comorbidity in HIV infection in Denmark. BMC Infect Dis [Internet]. **2016**; 16(1):713. Available from: http://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-016-2026-9
19. WHO. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies: Report of a WHO Expert consultation. Lancet. 2004.

ACCEPTED MANUSCRIPT

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20. JNC 8. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA [Internet]. **2014**; 311(5):507–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24352797
21. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J. Am. Coll. Cardiol. 2014. p. 2889–2934.
22. Min JK, Shaw LJ, Devereux RB, et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. J Am Coll Cardiol. United States; **2007**; 50(12):1161–1170.
23. Shah ASV, Stelzle D, Lee KK, et al. Global Burden of Atherosclerotic Cardiovascular Disease in People Living With HIV. Circulation. Lippincott Williams and Wilkins; **2018**; 138(11):1100–1112.
24. McKibben RA, Margolick JB, Grinspoon S, et al. Elevated levels of monocyte activation markers are associated with subclinical atherosclerosis in men with and those without HIV infection. J Infect Dis. **2015**; .
25. Weintraub WS, Spertus JA, Kolm P, et al. Effect of PCI on quality of life in patients with stable coronary disease. N Engl J Med. United States; **2008**; 359(7):677–687.
26. Maurovich-Horvat P, Bosserdt M, Kofoed KF, et al. CT or Invasive Coronary Angiography in Stable Chest Pain. N Engl J Med. United States; **2022**; 386(17):1591–1602.
27. Hsue PY. Mechanisms of Cardiovascular Disease in the Setting of HIV Infection. Can J Cardiol [Internet]. Canadian Cardiovascular Society; **2019**; 35(3):238–248. Available from: https://doi.org/10.1016/j.cjca.2018.12.024
28. Rasmussen LD, Helleberg M, May MT, et al. Myocardial infarction among danish HIV-infected individuals: Population-attributable fractions associated with smoking. Clin Infect Dis. **2015**; .
29. Gelpi M, Afzal S, Lundgren J, et al. Higher Risk of Abdominal Obesity, Elevated LDL Cholesterol and Hypertriglyceridemia, but not of Hypertension, in People Living with HIV: Results from the Copenhagen Comorbidity in HIV Infection (COCOMO) Study. Clin Infect Dis [Internet]. **2018**; (May):1–8. Available from: +
30. Ryom L, Miguel R De, Cotter AG, et al. Major revision version 11.0 of the European AIDS Clinical Society Guidelines 2021. HIV Med. England; **2022**; .
31. Triant VA, Perez J, Regan S, et al. Cardiovascular Risk Prediction Functions Underestimate Risk in HIV Infection. Circulation. **2018**; 137(21):2203–2214.
32. Friis-Moller N, Reiss P, Sabin CA, et al. Class of antiretroviral drugs and the risk of myocardial infarction. N Engl J Med. **2007**; .
33. Ryom L, Lundgren JD, El-Sadr W, et al. Cardiovascular disease and use of contemporary protease inhibitors: the D:A:D international prospective multicohort study. Lancet HIV. **2018**; .
34. Lundgren J, Mocroft A, Ryom L. Contemporary protease inhibitors and cardiovascular risk. Curr Opin Infect Dis. United States; **2018**; 31(1):8–13.
35. Knudsen AD, Graff C, Nielsen JB, et al. De novo electrocardiographic abnormalities in persons living with HIV. Sci Rep. **2021**; 11(1).
36. Kovari H, Calmy A, Doco-Lecompte T, et al. Antiretroviral Drugs Associated With Subclinical Coronary Artery Disease in the Swiss Human Immunodeficiency Virus Cohort Study. Clin Infect Dis. **2019**; .

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37. Hoffmann U, Lu MT, Foldyna B, et al. Assessment of Coronary Artery Disease With Computed Tomography Angiography and Inflammatory and Immune Activation Biomarkers Among Adults With HIV Eligible for Primary Cardiovascular Prevention. JAMA Netw open. **2021**; 4(6):e2114923.
38. Libby P, Loscalzo J, Ridker PM, et al. Inflammation, Immunity, and Infection in Atherothrombosis: JACC Review Topic of the Week. J Am Coll Cardiol. **2018**; 72(17):2071–2081.
39. Bandera A, Masetti M, Fabbiani M, et al. The NLRP3 Inflammasome Is Upregulated in HIV-Infected Antiretroviral Therapy-Treated Individuals with Defective Immune Recovery. Front Immunol. **2018**; 9:214.
40. Doitsh G, Galloway NLK, Geng X, et al. Cell death by pyroptosis drives CD4 T-cell depletion in HIV-1 infection. Nature. **2014**; 505(7484):509–514.

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