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HIV infection is associated with thoracic and abdominal aortic aneurysms: a prospective matched cohort study

Julie Høgh [1], Michael Huy Cuong Pham [2], Andreas Dehlbæk Knudsen [1,2], Rebekka Faber Thudium [1], Marco Gelpi [1], Per Ejlstrup Sigvardsen[2], Andreas Fuchs[2], Jørgen Tobias Kühl[2], Shoaib Afzal [3], Børge Grønne Nordestgaard [3,4], Thomas Benfield [4,5], Lars Køber [2,4], Jan Gerstoft[1,4], Klaus Fuglsang Kofoed [2,4,6], and Susanne Dam Nielsen [1,4]*

[1]Department of Infectious Diseases, Rigshospitalet, University of Copenhagen, Esther Møllers Vej 6, 2100 Kbh Ø, Copenhagen, Denmark; [2]Department of Cardiology, The Heart Center, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, 2100 Kbh Ø, Copenhagen, Denmark; [3]The Copenhagen General Population Study, Department of Clinical Biochemistry, Herlev Gentofte Hospital, Copenhagen University Hospital Herlev, Borgmester Ib Juuls Vej 1, 2730 Herlev, Denmark; [4]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Blegdamsvej 3B, 2200 Kbh N, Copenhagen, Denmark; [5]Department of Infectious Diseases, Copenhagen University Hospital, Amager Hvidovre, Kettegård Alle 30, 2650 Hvidovre, Denmark; and [6]Department of Radiology, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, 2100 Kbh Ø, Copenhagen, Denmark

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Aims Little is known about the prevalence of aortic aneurysms among people living with HIV (PLWH). We investigated whether HIV status is independently associated with having aortic aneurysms. Furthermore, we determined risk factors associated with aortic aneurysms in PLWH.

Methods and results PLWH aged ≥40 years ($n = 594$) were recruited from the Copenhagen Comorbidity in HIV Infection study and matched for age and sex with uninfected controls ($n = 1188$) from the Copenhagen General Population Study. Aortic dimensions were assessed using contrast enhanced computed tomography. Aortic aneurysms were defined according to the European Society of Cardiology guidelines, i.e. an aortic dilation of ≥50% or an infrarenal aortic diameter of ≥30 mm. Among PLWH and uninfected controls, the median (interquartile range) age was 52 (47–60) and 52 (48–61) and 88% and 90% were male, respectively. We found 46 aneurysms in 42 (7.1%) PLWH and 31 aneurysms in 29 (2.4%) uninfected controls ($P < 0.001$). PLWH had a significantly higher prevalence of ascending aortic aneurysms and infrarenal aortic aneurysms. In an adjusted model, HIV was independently associated with aortic aneurysms (adjusted odds ratio; 4.51 [95% confidence interval 2.56–8.08], $P < 0.001$). Within PLWH, obesity and hepatitis B co-infection were associated with aortic aneurysms.

Conclusion PLWH had four-fold higher odds of aortic aneurysms compared to uninfected controls, and HIV status was independently associated with aortic aneurysms. Among PLWH, age, obesity and hepatitis B co-infection were associated with higher odds of aortic aneurysms. Our findings suggest that increased attention to aortic aneurysms in PLWH may be beneficial.

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* Corresponding author. Tel: +45 3545 0859, Fax: +45 3545 6648, Email: sdn@dadlnet.dk
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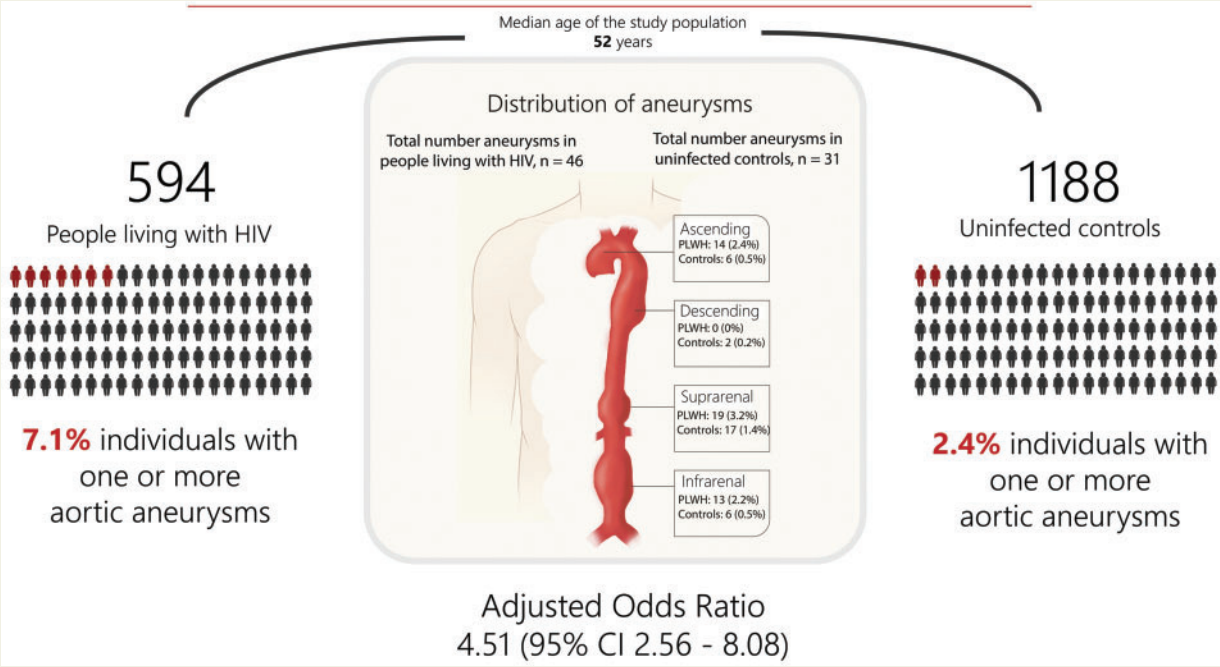
Graphical Abstract



People living with HIV have increased risk of aortic aneurysms compared to uninfected controls.

Keywords HIV • Aortic aneurysm • Syphilis • Comorbidity • Computed tomography imaging

Introduction

The introduction of combination antiretroviral therapy has dramatically improved the prognosis for people living with HIV (PLWH), but long-term survival remains lower among PLWH than among uninfected individuals.[1] This is partly explained by an increased incidence of cardiovascular disease (CVD),[2] and PLWH has been reported to be twice as likely to develop atherosclerotic CVD compared to the general population.[2,3]

Aortic aneurysms are pathological dilatations of an aortic segment with a diameter ≥50% greater than normal.[4] Aortic aneurysms are divided into thoracic aortic aneurysms and abdominal aortic aneurysms. When ruptured, abdominal aortic aneurysms have a mortality rate of around 80%,[5] whereas unruptured aneurysms generally are asymptomatic and in most cases diagnosed incidentally.[4] Screening of high-risk populations such as men aged >65 years is recommended.[6] Known risk factors for abdominal aortic aneurysms include age, male sex, smoking, family history of abdominal aortic aneurysms, atherosclerosis, hypercholesterolaemia, and hypertension.[4,7,8] Thoracic aortic aneurysms have been associated with hypertension, bicuspid aortic valves and genetic risk factors.[6] Several of these risk factors are common among PLWH.[9–11] Furthermore, a high proportion of PLWH in Europe and Northern America are men who have sex with men,[12] who are disproportionally burdened with syphilis infections.[13,14] Syphilis may also constitute a risk factor, especially for thoracic aortic aneurysms.[15,16] In addition to being associated with several risk factors for aortic aneurysms, HIV infection has been associated with cerebral aneurysmal vasculopathy.[17]

Although PLWH are at higher risk of CVD in general and may have several risk factors for aortic aneurysms, the burden of aortic aneurysms in PLWH is unknown, and no previous study has investigated whether HIV is a risk factor for aortic aneurysms. We aimed to determine the prevalence of aortic aneurysms among well-treated PLWH and uninfected controls using contrast enhanced computed tomography (CT).[18] Furthermore, we aimed to determine whether HIV is independently associated with prevalence of aortic aneurysms and to determine traditional, as well as HIV-specific risk factors, for aortic aneurysms among PLWH. We hypothesized that HIV would be independently associated with higher odds of aortic aneurysms. In addition, we hypothesized that traditional, as well as HIV-specific risk factors including previous or current syphilis infection, would be associated with higher odds of aortic aneurysms among PLWH.

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Methods

Study design and population

The Copenhagen Comorbidity in HIV Infection (COCOMO) study is a non-interventional, cohort study with the aim of assessing the burden of non-AIDS comorbidities in PLWH. Inclusion criteria were a positive HIV test and age >18 years. Between March 2015 and December 2016, the COCOMO study included 1099 participants, all living in the greater Copenhagen area. The procedures for recruitment and data collection have been described in detail elsewhere.[19] All participants of COCOMO were offered a combined thoracic and abdominal CT examination; CT examinations were performed from the study start in spring 2015 until November 2016. A total of 720 COCOMO participants had a contrast enhanced CT performed, of these 594 were 40 years or older. An overview of COCOMO participants 40 years or older with contrast enhanced CT vs. COCOMO participants without contrast enhanced CT is shown in Supplementary material online, *Table S1*. Participants with estimated glomerular filtration rate <30 mL/min/1.73 m^2 or chronic kidney disease were excluded due to risk associated with the use of contrast.

Uninfected controls were included from the Copenhagen General Population Study (CGPS), a non-interventional longitudinal study, including >110 000 participants residing in the greater Copenhagen area of whom >10 000 have had a combined thoracic and abdominal CT examination performed between 2010 and 2019.[20] As only CGPS participants older than 40 years were offered a CT examination, only COCOMO participants older than 40 years, with a contrast enhanced CT of both thorax and abdomen ($n = 594$), were matched by age and sex (in a 1:2 ratio) to participants in CGPS, with a contrast enhanced CT of both thorax and abdomen ($n = 6380$). Matching was performed using propensity score matching and the R-package 'MatchIt[21]'.

Ethical approval was obtained by the Regional Ethical Committee of Copenhagen (COCOMO: H-8-2014-004; CGPS: H-KF-01-144/01). The study was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Clinical characteristics and self-reported outcomes

A physical examination including anthropometrics and blood pressure measurements was performed by trained clinical staff using identical standard operating procedures in COCOMO and CGPS. Identical questionnaires were used to collect information regarding smoking, medical history, and medication. Non-fasting venous blood samples were collected and analysed for plasma high-sensitivity C-reactive protein (hsCRP), low-density lipoprotein cholesterol (LDL-C), glucose, and glycated haemoglobin (HbA1c). LDL-C was calculated using the Friedewald equation,[22] unless triglycerides were >4 mmol/L, and then LDL-C was measured directly. All blood samples from both COCOMO and CGPS participants were analysed in the same laboratory at Copenhagen University Hospital Herlev.[19] Furthermore, plasma concentration of interleukin-6 (IL-6) was measured using magnetic multiplex assay kits from R&D systems at the Department of Clinical Immunology, Rigshospitalet, Copenhagen, Denmark.

Data regarding HIV infection, such as mode of transmission, duration of HIV infection, type of antiretroviral therapy, and syphilis serology, were obtained from reviews of medical charts. All PLWH underwent annual screening for syphilis.

Active syphilis was defined as a combined positive screening nontreponemal test and a positive treponemal confirmatory test for previously uninfected and/or a four-fold or greater increase in titre of rapid plasma reagin. Prior syphilis was defined as positive treponemal test with negative rapid plasma reagin at time of CT scan.

We defined hypertension as current use of antihypertensive treatment and/or systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg.[23] Elevated LDL-C was defined as LDL-C ≥ 160 mg/dL (4.14 mM) and/or current lipid-lowering treatment.[24] Diabetes was defined as non-fasting plasma glucose ≥11.1 mmol/L (≥200 mg/dL) and/or HbA1c ≥48 mmol/mol (6.5%) and/or antidiabetic treatment. Body mass index (BMI) was defined according to the World Health Organization classification (<18.5 kg/m^2 underweight, 18.5–24.99 kg/m^2 normal weight, 25–29.99 kg/m^2 overweight, and ≥30 kg/m^2 obese).[25] Normal weight was used as reference. Injecting drug use (IDU) was defined as self-reported IDU. Hepatitis C virus co-infection was defined as positive hepatitis C virus RNA, and hepatitis B virus co-infection was defined as a positive hepatitis B virus surface-antigen. Cytomegalovirus status was defined according to cytomegalovirus-IgG. Low-grade inflammation was defined as hsCRP >1.39 mg/L as previously described.[26]

CT examinations

CT examinations were performed with a 320-detector CT scanner (Aquilion ONE, ViSION Edition, Canon Medical Systems, Otawara, Japan) at Rigshospitalet, Copenhagen University Hospital, using a uniform protocol for COCOMO and CGPS participants. Scanner settings were as follows: gantry rotation time 350 ms and detector collimation 0.5 × 320. Choice of tube voltage (100–120 kV) and current (280–500 mA) were based according to BMI.[27] An intravenous contrast agent (Visipaque 78 mL, 320 mg/mL) was infused with a flow rate of 5 mL/s followed by a saline chaser. First, a contrast enhanced thoracic angiography CT was performed using a region of interest set in the descending aorta with an automatic trigger-point at 250 Hounsfield units. Second, after a 10-s delay, the abdominal CT was performed. The thoracic contrast enhanced phase was reconstructed with a 0.5-mm slice thickness and increments of 0.25 mm. The abdominal contrast enhanced phase was reconstructed with a 3.0-mm slice thickness and increments of 3.0 mm.

Aortic analyses

On contrast-enhanced CT images, aortic diameters were measured at multiple anatomical points of the aorta, including the ascending aorta, descending aorta, aorta at the level of the coeliac trunk, and the infrarenal abdominal aorta as previously described.[27] All regional aortic measurements were performed perpendicular to the longitudinal axis of the aorta. Analyses of all CT images from both COCOMO and CGPS were performed using imaging analysis software (Vitrea Fx, version 6.9; Vital Images Inc., MN, USA) on dedicated workstations by two experienced readers (J.H. and M.H.C.P.) blinded to clinical characteristics, but not to HIV status. A non-biased third-party reader would determine the outcome in case of disagreement between the two readers. Inter- and intra-observer variability of the aortic measurements was previously reported and had a mean coefficient of variation of 2.8% and 2.4% at the ascending aorta, 5.6% and 2.8% at the descending aorta, 4.2% and 5.5% at suprarenal aorta, and 5.1% and 3.1% at infrarenal aorta.[27]

Aortic aneurysms were defined as one or more aneurysms according to the European Society of Cardiology guidelines; i.e. an aortic dilation ≥50% larger in diameter compared to the expected normal diameter or an infrarenal diameter ≥30 mm^6 measured as the maximal external aortic diameter.[28] Accordingly, aneurysms were defined as an ascending aorta diameter ≥45 mm and/or descending aorta diameter ≥35 mm and/or suprarenal abdominal aorta diameter ≥30 mm and/or infrarenal abdominal aorta diameter ≥30 mm.[29] Aortic aneurysm wall thickness was defined as the difference between maximal external aortic aneurysm diameter and maximal internal aortic aneurysm diameter. Aortic aneurysms were

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Table 1 Demographic and clinical characteristics of the study population

Variable	People living with HIV (*n* = 594)	Uninfected controls (*n* = 1188)	*P*-value
Age, median [IQR]	52 [47–60]	52 [48–61]	
Male, *n* (%)	523 (88)	1065 (90)	
European origin, *n* (%)	508 (87)	1,187 (100)	<0.001
BMI, mean (SD)	25 (3.5)	26 (3.4)	<0.001
BMI classification, *n* (%)			<0.001
Underweight	14 (2.4)	5 (0.4)	
Normal weight	309 (52)	422 (35.5)	
Overweight	224 (38)	590 (50)	
Obesity	44 (7)	167 (14)	
Smoking status, *n* (%)			<0.001
Never smoker	196 (33)	599 (50)	
Current smoker	158 (27)	133 (11)	
Previous smoker	227 (38)	446 (38)	
Diabetes, *n* (%)	20 (3)	28 (2)	0.248
Hypertension, *n* (%)	275 (46)	508 (43)	0.548
Hyperlipidaemia, *n* (%)	53 (9)	171 (14)	0.012
LDL-C, median [IQR]	2.8 [2.2–3.5]	3.1 [2.5–3.8]	<0.001
Lipid-lowering agents	80 (13)	95 (8)	<0.001

classified as either fusiform, concentric saccular, or eccentric saccular by both readers. Furthermore, both readers evaluated if the aortic aneurysms had calcification. Participants with aneurysms meeting the clinical threshold for surgical repair according to the Danish and European guidelines[6,30] were referred for clinical evaluation.

Statistics

The sample size was based on a priori power calculations. Assuming a prevalence of aortic aneurysms in the general population of 4%, inclusion of 650 PLWH and 1300 controls in a 1:2 matching would have allowed us to show an odds ratio (OR) of 1.8 with a power of 0.8 ($\alpha = 0.05$). The number of PLWH aged ≥40 years with contrast enhanced CT imaging was slightly lower than anticipated. With 594 PLWH and 1188 uninfected controls, we were able to show an OR of 1.9 with a power (1 - β) of 0.8 ($\alpha = 0.05$).

Power calculations were performed using the epiR package[31] in R and assuming two-tailed *P*-values.

Descriptive statistical analyses were used to assess demographics, risk factors, and physical measurements. Groups were compared using *t*-test or Mann–Whitney *U* test for continuous data and χ^2 tests or Fisher's exact test for categorical data. Continuous data were reported with means and standard deviations for normal deviates and medians with interquartile ranges (IQR) for variables not normally distributed as appropriate. For categorical data, frequency counts and percentage were reported.

We investigated the association between HIV and aortic aneurysms using simple and multivariable logistic regression. We used a predefined model and adjusted for age, sex, hypertension, hyperlipidaemia, origin, smoking status (previous/current/never smoker), and BMI category. Analyses were performed as patient-level analysis, and aortic aneurysm in the model was defined as the number of participants with aortic aneurysms.

Within PLWH, we investigated the association between traditional risk factors (age, sex, hypertension, hyperlipidaemia, origin, smoking status and BMI category) as well as HIV-specific risk factors (CD4+, CD4+/CD8+ ratio, viral load >50 copies/mL, nadir CD4+ <200 cells/μL, years with HIV infection, years on combined antiretroviral therapy, use of protease inhibitors, use of integrase inhibitors, use of nucleoside/nucleotide reverse transcriptase inhibitors, use of non-nucleoside reverse transcriptase inhibitors, previous or current syphilis, previous AIDS defining condition, or IDU) and aortic aneurysms in a model adjusted for age, sex, hypertension, hyperlipidaemia, origin, smoking status, and BMI category. In addition, within uninfected controls we investigated the association between traditional risk factors and aortic aneurysms using the same predefined model.

In exploratory analyses, we determined the prevalence of abdominal aortic aneurysms among men 65 years or older, who are considered a high-risk population. Additionally, interaction between HIV and ageing was tested in our predefined multivariable model with aortic aneurysms as the dependent variable. The association between HIV and the aortic aneurysm wall thickness was investigated for each anatomic site separately using linear regression adjusting for our predefined model.

In further exploratory analyses, we investigated the association between hepatitis B virus, hepatitis C virus, cytomegalovirus, cumulative pack years of smoking, IL-6, and hsCRP >1.39 mg/L and aortic aneurysms in PLWH adjusting for the predefined multivariable model described above.

In sensitivity analysis of participants with European origin, we investigated the association between HIV and aortic aneurysms using multivariable logistic regression adjusting for age, sex, hypertension, hyperlipidaemia, smoking status (previous/current/never smoker), and BMI category. In another sensitivity analysis we investigated the association between HIV and aortic aneurysms in a multivariable model including important confounders as continuous measures. Accordingly, we included age, BMI, systolic blood pressure and pulse pressure as continuous measures and sex, smoking status, antihypertensive treatment, hyperlipidaemia, and origin as categorical measures.

A *P*-value of <0.05 was considered statistically significant. All *P*-values were two-sided. Missing data were excluded from the calculations by casewise/listwise deletion (Supplementary material online, *Tables S2 and S3*). All statistical analyses were conducted using R Statistics 3.6.1 (R Core Team, Vienna, Austria).[32] Figures were made using R ggplot2.[33]

Results

Of 1099 PLWH included in the COCOMO study, 720 had a contrast enhanced CT performed. Of these, 594 were older than 40 years and included along with 1188 matched, uninfected controls. Characteristics of the participants are listed in *Table 1* and HIV-related variables are listed in *Table 2*. The median (IQR) age for PLWH and uninfected controls was 52 (47–60) and 52 (48–61), respectively. The majority of PLWH (87%) and all uninfected controls (100%) were of European origin. Among PLWH, 587 (98.8%) were on antiretroviral therapy and median (IQR) time since HIV diagnosis was 15 (8–23) years. At the time of CT, 9 (2%) PLWH had current syphilis infection and 195 (33%) had previous syphilis infection.

An overview of missing demographic and clinical variables is given in Supplementary material online, *Table S2*.

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Table 2 HIV-specific variables for people living with HIV included in the study ($n = 594$)

Variable	People living with HIV (n=594)
Transmission mode, *n* (%)	
MSM	430 (72)
Heterosexual	124 (21)
IDU	7 (1.2)
Others	34 (6)
Current $CD4^+$, cells/μL, median [IQR]	679 [513–870]
<200	7 (1.2)
200–349	36 (6)
350–499	85 (14)
≥500	378 (63)
$CD4^+$ nadir <200, cells/μL, *n* (%)	246 (42)
$CD4^+/CD8^+$ ratio, median [IQR]	0.8 [0.6–1.1]
Time since HIV diagnosis, years, median [IQR]	15 [8–23]
History of AIDS (yes), *n* (%)	112 (19)
Time on cART treatment, years, median [IQR]	13 [6–18]
Currently on cART, *n* (%)	587 (98.8)
Viral load >50 copies/mL, *n* (%)	23 (4)
Syphilis infection	
Never syphilis	387 (65)
Previous syphilis infection	195 (33)
Current syphilis infection	9 (2)
Cytomegalovirus co-infection, *n* (%)	303 (51)
Hepatitis B virus co-infection, *n* (%)	18 (3)
Hepatitis C virus co-infection, *n* (%)	33 (6)
hsCRP, mg/L, median [IQR]	1.2 [0.6–2.4]
IL-6, pg/mL, median [IQR]	3.4 [2.5–4.6]
IDU, *n* (%)	12 (2)

cART, combined antiretroviral therapy; hsCRP, high-sensitivity C-reactive protein; IDU, injecting drug use; IL-6, interleukin 6; MSM, men who have sex with men.

Prevalence of aortic aneurysms in PLWH and uninfected controls

We found 46 aneurysms in 42 (7.1%) PLWH and 31 aneurysms in 29 (2.4%) uninfected controls ($P < 0.001$). In our study, two PLWH were referred for clinical evaluation, even though their aneurysms did not meet the surgical threshold. One of these participants was later operated due to an ascending aortic aneurysm and a bicuspid aortic valve. There were four cases of bicuspid aortic valves, two among PLWH and two among the uninfected controls. All observed aortic aneurysms in both groups were in males. An overview of missing aortic measurements is given in Supplementary material online, *Table S3*. The distribution of aortic aneurysms is listed in *Table 3*. PLWH had a higher prevalence of ascending, suprarenal, and infrarenal aortic aneurysms, but not of descending aortic aneurysms, than uninfected controls. In PLWH, we found 23% ($n = 3$) of infrarenal aortic aneurysms to be concentric saccular and in uninfected controls, we found 17% ($n = 1$) of infrarenal aortic aneurysms to be concentric saccular. All other aortic aneurysms were classified as fusiform (Supplementary material online, *Table S4*). We found no significant difference in classification of aneurysms between PLWH and uninfected controls.

When investigating calcification of the aortic aneurysms, we found 100% of infrarenal aortic aneurysms, 26% of suprarenal aortic aneurysms, and 0% of ascending aortic aneurysms to have calcification (Supplementary material online, *Table S4*).

The prevalence of abdominal aortic aneurysms (suprarenal and infrarenal abdominal aneurysms) among men in different age groups is listed in *Table 4*. For men older than the recommended screening threshold (>65 years of age), suprarenal and infrarenal aortic aneurysms were the most frequent aneurysms among both PLWH and uninfected controls. The prevalence of abdominal aortic aneurysms was 13 (18.1%) among PLWH ($n = 72$) and 14 (8.6%) among the uninfected controls ($n = 163$).

Risk factors associated with aortic aneurysms in PLWH and uninfected controls

The crude OR of aortic aneurysms among PLWH compared to uninfected controls was 3.04 (95% CI 1.87–4.93; $P < 0.001$) (*Figure 1*). In a multivariable model adjusted for age, sex, BMI category, smoking status, hypertension, hyperlipidaemia and origin, the adjusted OR (aOR) of aortic aneurysms among PLWH compared to uninfected controls was 4.51 (95% CI 2.56–8.08; $P < 0.001$) (*Figure 1*, *Graphical abstract*).

The association between HIV and aortic aneurysms was similar across age groups (*P*-interaction = 0.503).

The median (IQR) ascending aortic aneurysm wall thickness was 2.6 mm (2.4–2.9) in PLWH and 2.1 mm (2.0–2.3) in uninfected controls ($P = 0.010$). For suprarenal aortic aneurysms, median (IQR) wall thickness was 2.6 mm (2.3–3.3) in PLWH and 2.3 mm (2.2–2.8) in uninfected controls ($P = 0.409$), and for infrarenal aortic aneurysms median (IQR) wall thickness was 3.0 mm (2.6–7.1) in PLWH and 1.9 mm (1.7–2.0) in uninfected controls ($P = 0.027$). When investigating the association between HIV and wall thickness of aortic aneurysms, using linear regression models, we found PLWH to have significantly thicker aortic walls in ascending aortic aneurysms (0.62 mm, [95% CI 0.26–0.97], $P = 0.008$). However, HIV infection was not associated with suprarenal and infrarenal aortic aneurysm wall thickness.

In a sensitivity analysis, we investigated the association between HIV and aortic aneurysms among participants of European origin (PLWH: $n = 508$, uninfected controls: $n = 1188$). In a multivariable model, the aOR of aortic aneurysms among European PLWH compared to European uninfected controls was 4.58 (95% CI 2.57–8.14; $P < 0.001$). Additionally, in another sensitivity analysis, we investigated the association between HIV and aortic aneurysms in a multivariable model adjusted for important confounders as continuous measures, and found HIV to be associated with an increased OR of 5.60 (95% CI 2.55–12.31; $P < 0.001$) of aortic aneurysms compared to uninfected controls.

Risk factors associated with aortic aneurysms in PLWH

In analyses restricted to PLWH, traditional risk factors associated with aortic aneurysms included age (aOR 3.25 per decade, 95% CI 2.13–4.95; $P < 0.001$) and obesity (aOR 5.12, 95% CI 1.44–18.24; $P = 0.012$). Hypertension, smoking status, cumulative pack years,

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Table 3 Prevalence of aortic aneurysms in people living with HIV and uninfected controls

Variable	People living with HIV (n = 594)		Uninfected controls (n = 1188)		P-value
	n (% of group)	Distribution of aneurysms (% of total number of aneurysms)	n (% of group)	Distribution of aneurysms (% of total number of aneurysms)	
Total number of aneurysms	46 (7.7)		31 (2.6)		<0.001
Total number of people with aneurysms	42 (7.1)		29 (2.4)		<0.001
People with one aneurysm	38 (6.4)		27 (2.3)		
People with two aneurysms	4 (0.7)		2 (0.2)		
Thoracic aortic aneurysms					
Ascending aortic aneurysms	14 (2.4)	30%	6 (0.5)	19%	0.001
Descending aortic aneurysms	0 (0.0)	0%	2 (0.2)	7%	0.802
Abdominal aortic aneurysms					
Suprarenal aortic aneurysms	19 (3.2)	41%	17 (1.4)	55%	0.020
Infrarenal aortic aneurysms	13 (2.2)	28%	6 (0.5)	19%	0.003

origin, and hyperlipidaemia were not associated with aortic aneurysms in PLWH. In the analysis investigating the association between traditional risk factors and aortic aneurysms within uninfected controls, only age (aOR 2.38 per decade, 95% CI 1.58–3.61; $P < 0.001$) was associated with aortic aneurysms.

When investigating HIV-specific risk factors, only co-infection with hepatitis B virus was associated with higher odds of aortic aneurysms (aOR 5.57, 95% CI 1.47–21.12; $P = 0.012$). Other HIV-specific risk factors including previous or current syphilis, years with HIV infection, years on combination antiretroviral therapy, co-infection with hepatitis C virus, IDU, IL-6, hsCRP >1.39 mg/L, viral load >50 copies/mL, and nadir CD4+ <200 copies cells/μL were not associated with aortic aneurysms. An overview of the association between clinical and demographic variables and specific anatomic aneurysm sites is given in Supplementary material online, *Table S5*.

Discussion

In a large cohort of PLWH and uninfected controls, PLWH had a higher prevalence of aortic aneurysms, and HIV status was independently associated with 4.51 (95% CI 2.56–8.08) higher odds of aortic aneurysms after adjusting for traditional risk factors. In addition, age, obesity, and co-infection with hepatitis B virus were significantly associated with higher odds of aortic aneurysms among PLWH. Other traditional and HIV-specific risk factors including syphilis were not found. Our findings suggest that HIV infection is an independent risk factor for aortic aneurysms.

The prevalence of aortic aneurysms in uninfected men aged 65–74 years was comparable to that in the larger DANCAVAS study.[29] In our study, uninfected men aged ≥65 years had a slightly higher prevalence of abdominal aortic aneurysms of 8.6%, but men with HIV aged ≥65 years had a prevalence of abdominal aortic aneurysms that was two times higher than that. A similar prevalence was found among men with HIV who were around 15 years their junior (*Table 4*). We found infrarenal aortic aneurysms to be more frequent in persons aged ≥65 years in both PLWH and uninfected controls, a finding that is consistent with the general understanding of infrarenal aortic aneurysms being a regenerative disease of ageing. Screening for aortic aneurysms in men aged ≥65 years is recommended.[6] Furthermore, in men aged 65 years with a subaneurysmal abdominal aortic diameter (23–29 mm), 28% may develop an abdominal aortic aneurysm larger than the clinical threshold for surgery (≥55 mm) within 15 years.[34] Accordingly, even though the vast majority of PLWH had aneurysms below the surgical threshold, it is likely that some of the PLWH will need surgical repair at some point. As we found a higher prevalence of abdominal aortic aneurysms among male PLWH aged 65 years and screening of men aged ≥65 years is considered cost beneficial,[35,36] our findings suggest that screening for aortic aneurysms in PLWH may also be beneficial. This should be investigated in larger prospective trials with clinical endpoints.

When investigating traditional risk factors for aortic aneurysm, only age and obesity were found to be associated with aortic aneurysms. The Physicians' Health Study has previously described obesity as a significant risk factor for abdominal aortic aneurysms[37] and in Danish subjects body size has been closely associated with aortic diameter.[27] Furthermore, age is a well-described risk factor for aortic aneurysms.[7,29] Accordingly, we found the risk of aortic aneurysms to increase with age both among PLWH and uninfected controls. Smoking and hypertension are also considered risk factors for aortic aneurysms.[4,7] We did not find either to be associated with aneurysms in PLWH. However, 37% of PLWH with hypertension was on antihypertensive treatment which may reduce the effect of hypertension on aneurysm growth[38,39] and explain why we did not find an association between hypertension and aortic aneurysms. We tested both smoking status and cumulative pack years, but none of them were associated with aortic aneurysms in our population of PLWH. Male sex is also a well-described risk factor for aortic aneurysms.[7] In this study, we only observed aneurysms among men, and we were not able to determine the effect of sex. We might have found more

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Table 4 Prevalence of aortic aneurysms among men in different age groups

	People living with HIV		Uninfected controls	
	50–65 years (n = 252)	>65 years (n = 72)	50–65 years (n = 504)	>65 years (n = 163)
Thoracic aortic aneurysm, % (n)	2.4% (6)	6.9% (5)	0.8% (4)	1.8% (3)
Ascending aortic aneurysm	2.4% (6)	6.9% (5)	0.6% (3)	1.2% (2)
Descending aortic aneurysms	0% (0)	0% (0)	0.2% (1)	0.6% (1)
Abdominal aortic aneurysms, % (n)	7.1% (18)	18.1% (13)	1.6% (8)	8.6% (14)
Suprarenal aortic aneurysm	4.7% (12)	9.7% (7)	1.4% (7)	6% (10)
Infrarenal aortic aneurysms	2.4% (6)	9.7% (7)	0.2% (1)	3.1% (5)

Prevalence of abdominal and thoracic aortic aneurysms is calculated as prevalence of people with aortic aneurysms.

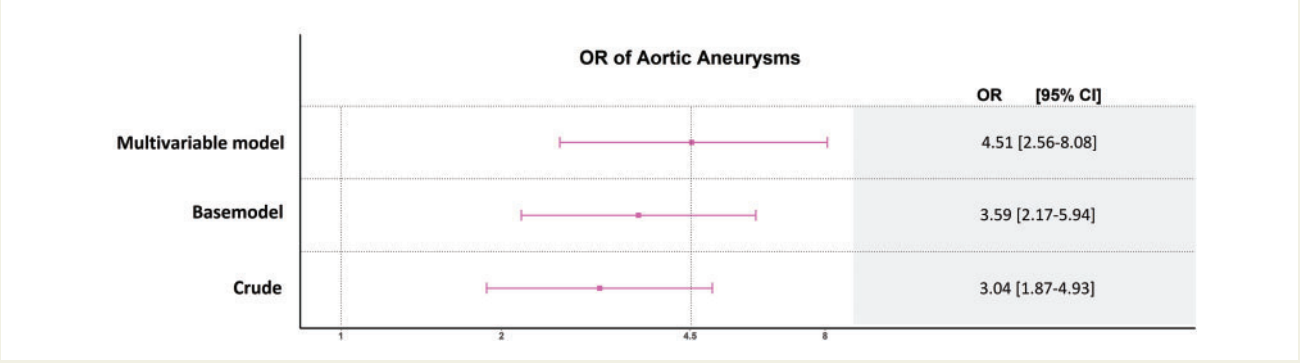

Figure 1 Basemodel is adjusted for age and sex. Multivariable model is adjusted for age, sex, body mass index category, smoking status, hypertension, hyperlipidaemia, and origin.

aneurysms among women if we had used cut-offs that were age, sex, and body size specific, but whether this would be clinically significant is unknown.

Development of aortic aneurysms has been closely associated with chronic inflammation and atherosclerosis,[8,40] though it is unclear whether the association is causative or the result of common risk factors such as smoking and hypertension.[4,7,8,40] We found 100% of infrarenal and 26% of suprarenal aortic aneurysms to have calcification, which supports that atherosclerosis is particularly associated with abdominal aortic aneurysms.[41] HIV has previously been associated with increased risk of atherosclerosis,[9,11,42] accordingly this association might be particularly important for the development of infrarenal aortic aneurysms. Furthermore, even in patients with relative preserved $CD4^+$ counts and undetectable viral load, HIV has been associated with chronic inflammation and immune activation,[43,44] and elevated inflammatory markers in PLWH have been associated with cardiovascular disease.[45,46] Chronic inflammation is thought to lead to the development of aortic aneurysms through alterations of the connective tissue in the aortic wall.[8] These inflammatory changes are thought to be associated with aortic wall thickening.[41] We found PLWH to have significantly thicker aortic walls in ascending aortic aneurysms, but not in suprarenal or infrarenal aortic aneurysms. One could therefore speculate that particularly ascending aortic aneurysms in PLWH are associated with chronic inflammation. We found hepatitis B virus co-infection to be associated with increased odds of aortic aneurysms. In analyses investigating the association between variables and specific aneurysm sites (Supplementary material online, *Table S5*), we found hepatitis B co-infection to be significantly associated with increased odds of suprarenal aortic aneurysms. However, we only included 18 PLWH with hepatitis B virus co-infection, and therefore the association between hepatitis B virus and aortic aneurysms may be an incidental finding. Hepatitis B infection has been associated with increased risk of cerebral aneurysm rupture,[47] but not with aneurysm development. Furthermore, in a larger study, co-infection with hepatitis B virus in PLWH was not found to be associated with risk of CVD.[48] Therefore, the association between hepatitis B infection and aortic aneurysm development should be investigated in a larger population of people with hepatitis B infection. In addition, in multivariable models we tested low nadir CD4+ and found no association with aortic aneurysms. This indicates that prior immunodeficiency is not the driver of aortic aneurysms in PLWH. The COCOMO cohort consists of mainly well-treated PLWH. Thus, 98.8% were on combination antiretroviral therapy and 96% had undetectable viral replication. As such, we had limited power to determine any impact of ongoing viral replication. Chronic low-grade inflammation is a feature of HIV infection even in well-treated cohorts. This is also the case for the COCOMO cohort.[44] However, we did not find significant associations between markers of inflammation including IL-6 and hsCRP and aortic aneurysms in PLWH. In obese mice, the inflammatory marker IL-18 has been associated with aneurysm development, which links inflammation, obesity and aneurysm development.[49]

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Previous studies have found syphilis to be associated with aortic aneurysms, especially in the ascending aorta.[15,16] Danish PLWH are screened for syphilis once a year, and treatment for active infection is administered promptly and free of charge. Consequently, although a third of PLWH had signs of previous infection, few may have had untreated syphilis for a longer time period. It could be that only prolonged or tertiary syphilis composes a risk factor for aortic aneurysms, and we cannot rule out that syphilis constitutes a risk factor for aortic aneurysms in other populations of PLWH with limited access to screening and treatment. In addition, specific types of antiretroviral therapy have previously been associated with CVD in PLWH living in Copenhagen,[50,51] but we did not find this association with aortic aneurysms.

There were limitations to this study. First, the study is cross-sectional, which prevents us from drawing any conclusions regarding causality. Second, study participants were predominantly men and we observed no aneurysms among women in either PLWH or controls. Therefore, we cannot describe sex-specific differences in the association between HIV and aortic aneurysms. Third, we only included 18 PLWH with hepatitis B virus co-infection, and therefore the association between hepatitis B virus and aortic aneurysms might be an incidental finding. Fourth, the ethnic distribution differed between PLWH and controls, but since origin was not associated with aortic aneurysms and the association between HIV and aortic aneurysms was unaltered in a sensitivity analysis of only participants with European origin, the significance of this is of limited impact. Fifth, readers of CT scans were not blinded to HIV status.

Strengths of the study include size of the study sample and a uniform approach to data collection in PLWH and controls. Furthermore, both PLWH and uninfected controls were included from the same geographical area in the same period. In addition, aortic aneurysms were assessed using gold standard CT scans and both groups had CT scans performed on the same CT scanner using a uniform protocol for image acquisition and analysis.

In conclusion, well-treated PLWH had higher prevalence of aortic aneurysms than uninfected controls, and HIV was independently associated with higher odds of aortic aneurysms. Among PLWH, age, obesity, and hepatitis B co-infection were associated with higher odds of aortic aneurysms. Our findings suggest that increased attention to aortic aneurysms in PLWH is warranted.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Contributions

J.H. was responsible for concept, CT analyses, and statistical analyses and drafted the manuscript. M.H.C.P. was responsible for concept and CT analyses and edited the manuscript. A.D.K., R.F.T., and M.G. were responsible for concept and statistical analysis and edited the manuscript. P.E.S., A.F., J.T.K., T.B., L.K., J.G., and K.F.K. were responsible for concept and edited the manuscript. S.A., B.G.N., and S.D.N. were responsible for concept and data collection and edited the manuscript.

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Data availability

The data underlying this article cannot be shared publicly as this has been stated in the approvals from the ethical committee and data protection agency . The data will be shared and can be accessed at our institution on reasonable request to the corresponding author.

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