

Higher Risk of Abdominal Obesity, Elevated Low-Density Lipoprotein Cholesterol, and Hypertriglyceridemia, but not of Hypertension, in People Living With Human Immunodeficiency Virus (HIV): Results From the Copenhagen Comorbidity in HIV Infection Study

Marco Gelpi,¹ Shoaib Afzal,² Jens Lundgren,^{1,3} Andreas Ronit,¹ Ashley Roen,⁴ Amanda Mocroft,⁴ Jan Gerstoft,¹ Anne-Mette Lebech,¹ Birgitte Lindegaard,⁵ Klaus Fuglsang Kofoed,⁶ Børge G. Nordestgaard,^{2,7} and Susanne Dam Nielsen¹

¹Viro-immunology Research Unit, Department of Infectious Diseases 8632, Rigshospitalet, University of Copenhagen, ²The Copenhagen General Population Study, Department of Clinical Biochemistry, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, and ³CHIP, Department of Infectious Diseases 8632, Rigshospitalet, University of Copenhagen, Denmark; ⁴HIV Epidemiology and Biostatistics Unit, Department of Infection and Population Health, University College London, London, United Kingdom; and ⁵Center for Inflammation and Metabolism, Rigshospitalet, ⁶Department of Cardiology, Rigshospitalet and ⁷Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

Background. People living with human immunodeficiency virus (PLWH) are characterized by excess risk of cardiovascular diseases (CVD) and CVD risk factors compared to uninfected individuals. We investigated the association between HIV infection and abdominal obesity, elevated low-density lipoprotein cholesterol (LDL-C), hypertriglyceridemia, and hypertension in a large cohort of predominantly well-treated PLWH and matched controls.

Methods. 1099 PLWH from the Copenhagen Co-morbidity in HIV Infection Study and 12 161 age- and sex-matched uninfected controls from the Copenhagen General Population Study were included and underwent blood pressure, waist, hip, weight, and height measurements and nonfasting blood samples. We assessed whether HIV was independently associated with abdominal obesity, elevated LDL-C, hypertriglyceridemia, and hypertension using logistic regression models adjusted for known risk factors.

Results. HIV infection was associated with higher risk of abdominal obesity (adjusted odds ratio [aOR], 1.92 [1.60–2.30]) for a given body mass index, elevated LDL-C (aOR, 1.32 [1.09–1.59]), hypertriglyceridemia (aOR, 1.76 [1.49–2.08]), and lower risk of hypertension (aOR, 0.63 [0.54–0.74]). The excess odds of abdominal obesity in PLWH was stronger with older age (*p* interaction, 0.001). Abdominal obesity was associated with elevated LDL-C (aOR, 1.44 [1.23–1.69]), hypertension (aOR, 1.32 [1.16–1.49]), and hypertriglyceridemia (aOR, 2.12 [1.86–2.41]).

Conclusions. Abdominal obesity was associated with proatherogenic metabolic factors including elevated LDL-C, hypertension, and hypertriglyceridemia and remains a distinct HIV-related phenotype, particularly among older PLWH. Effective interventions to reduce the apparent detrimental impact on cardiovascular risk from this phenotype are needed.

Keywords. HIV infection; abdominal obesity; elevated LDL cholesterol; hypertension; hypertriglyceridemia.

With the introduction of combination antiretroviral therapy (cART), people living with human immunodeficiency virus (PLWH) have experienced a dramatic improvement in life expectancy [1]. Nonetheless, the observed median survival time from age 50 years is still lower in PLWH than in uninfected individuals [2]. This is partly explained by an increased risk of cardiovascular diseases (CVD) [3], the biggest contributor to non-AIDS mortality in PLWH [4], as well as by diseases

or traits that constitute the metabolic syndrome (eg, abdominal obesity, dyslipidemia, hypertension, and diabetes) [3, 5–7].

The redistribution of body fat from the periphery toward the abdomen (fat redistribution syndrome) is a well-known feature of HIV infection, first defined in 1998 [8] and traditionally described as an important complication of old-generation antiretroviral treatment [8]. Abdominal obesity has been linked to higher risk of CVD and CVD risk factors in PLWH [9]. Due to new-generation cART with fewer metabolic complications, the incidence of fat redistribution syndrome has declined [10]. However, the exact mechanisms behind this condition are still unclear. In addition to cART [11], both host- [11] and viral-associated factors [12] may be involved. Whether fat redistribution syndrome is still involved in the excess risk of CVD in PLWH after the introduction of new antiretroviral regimens is yet to be determined.

Received 15 December 2017; editorial decision 4 February 2018; accepted 15 February 2018; published online February 17, 2018.

Correspondence: S. D. Nielsen, Viro-immunology Research Unit, Department of Infectious Diseases 8632, Copenhagen University Hospital, Blegdamsvej 9B, DK-2100 Copenhagen Ø, Denmark (sdn@dadlnet.dk).

Clinical Infectious Diseases® 2018;67(4):579–86

© The Author(s) 2018. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com. DOI: 10.1093/cid/ciy146

We tested the hypothesis that PLWH had a higher prevalence of abdominal obesity, elevated low-density lipoprotein cholesterol (LDL-C), hypertriglyceridemia, and hypertension and that HIV infection was independently associated with these outcomes. For this purpose, we investigated the prevalence of abdominal obesity, elevated LDL-C, hypertriglyceridemia, and hypertension in a large cohort of PLWH ($n = 1099$) compared to matched uninfected individuals ($n = 12\,161$); assessed whether HIV infection was independently associated with the risk of abdominal obesity, elevated LDL-C, hypertriglyceridemia, and hypertension; and aimed to identify HIV-associated predictors of these outcomes.

METHODS

Study Population

The Copenhagen Co-morbidity in HIV Infection (COCOMO) Study is a longitudinal 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, 1099 participants were enrolled in the study, representing more than 40% of the PLWH population residing in the Copenhagen area. The procedures for recruitment and data collection have been described elsewhere [13].

A total of 12 161 uninfected individuals were recruited from the Copenhagen General Population Study (CGPS), which is an ongoing population study initiated in 2003 that includes more than 100 000 individuals who reside in the greater Copenhagen area [14–17]. Of all the residents, 25% of those aged 20–40 years and 100% of those aged >40 years are invited to participate (response rate approximately 45%). Ethical approval was obtained by the Regional Ethics Committee of Copenhagen (COCOMO, H-15017350; CGPS, H-KF-01-144/01). Written informed consent was obtained from all participants.

Uninfected controls were frequency matched with PLWH by gender and 5 age year strata, and 14 randomly selected controls were identified for every woman and most men with HIV. For men aged 25–50 years, it was only possible to identify 3 to 11 controls in each 5-year age interval due to differences in the age- and sex-distribution between the HIV and control populations (Supplementary Figure 2).

Clinical Assessments

Information about participants' demographics, physical activity, education level, smoking history, and medication use were collected using an identically structured questionnaire for COCOMO and CGPS participants. Data regarding HIV infection were obtained from review of medical charts of COCOMO participants [13].

Trained clinic staff performed all examinations using identical protocols in both groups. Waist and hip measurements and body mass index (BMI) calculations were performed according to World Health Organization (WHO) guidelines [18]. Using

an automatic digital blood pressure (BP) monitor [19], BP was measured on the left arm after 5 minutes rest with the participant in the sitting position. Nonfasting venous blood was collected and analyzed for LDL-C, triglycerides, total cholesterol, HbA1c, and glucose. Blood samples from both COCOMO and CGPS participants were analyzed at Herlev Hospital, Copenhagen [13].

Outcome Definitions

According to WHO guidelines, abdominal obesity was defined as waist-to-hip ratio ≥ 0.90 for men and ≥ 0.85 for women [18].

According to American College of Cardiology–American Heart Association guidelines, elevated LDL-C was defined as LDL ≥ 4.14 mmol/L and/or lipid-lowering therapy [20]. As sensitivity analysis, a cutoff of LDL ≥ 3.00 mmol/L according to European guidelines was used [21]. According to Joint National Committee guidelines, hypertension was defined as antihypertensive treatment and/or having ≥ 40 mm Hg systolic and/or ≥ 90 mm Hg diastolic BP values [22]. Hypertriglyceridemia was defined as triglycerides ≥ 2 mmol/L and/or lipid-lowering therapy [21]. Metabolic syndrome was defined using a slightly modified version of the harmonized metabolic syndrome definition [17, 23]. These criteria are depicted in Table 1.

Statistical Analyses

Continuous variables were reported as median (interquartile range), and categorical variables were reported as percentage and frequency. Different groups were compared with *t* test or Mann Whitney U test for continuous data that had normal or nonnormal distribution, respectively, and χ^2 and Fisher tests for categorical data.

Multivariable logistic models were fit to test associations between HIV infection and the outcomes of interest. Unadjusted and adjusted odds ratios (OR and aOR) and 95% confidence intervals were computed. Covariates included in the model were age, gender, smoking history (current, former, never smoker), origin (Scandinavian, other European Union, Middle-East and Indian subcontinent, other), educational level (none, short, vocational, middle length, university), physical activity (inactive, moderately inactive, moderately active, very active), BMI, and abdominal obesity.

Separate models for PLWH were fit to assess associations between HIV-related variables and each outcome. The following 2 models were considered: in model 1, abdominal obesity was used as an dependent variable. Independent variables included in model 1 were age, gender, smoking history, physical activity, origin, education, BMI, current CD4, CD4 nadir <200 , current viral load <40 copies, time since HIV infection and cART initiation, and hepatitis C coinfection. Model 2 was used when testing elevated LDL-C, hypertriglyceridemia, and hypertension as dependent variables. Independent variables included in the model were model 1 + abdominal obesity.

Table 1. Demographic and Clinical Characteristics of the Study Population

General Characteristic	People Living With Human Immunodeficiency Virus, n = 1099	Controls n = 12 161	P Value
Age median years, (IQR)	50.1 (42.8–58.0)	52.2 (45.7–61.0)	< .001
Gender male, % (n)	85.3 (937)	81.4 (9893)	.001
Origin, % (n)			< .001
Scandinavia	72.9 (788)	89.3 (10734)	...
Other European Union	11.9 (129)	6.9 (826)	...
Middle East and Indian subcontinent	1.8 (19)	3.1 (376)	...
Other	13.4 (145)	0.7 (90)	...
Smoking status, % (n)			< .001
Never smoker	33.6 (369)	48.0 (5839)	...
Current smoker	28.8 (317)	13.0 (1580)	...
Ex-smoker	34.0 (374)	38.5 (4679)	...
Education level, % (n)			< .001
None	11.6 (119)	7.0 (456)	...
Short	9.9 (102)	7.6 (490)	...
Vocational	29.3 (301)	34.3 (2221)	...
Middle length	22.7 (233)	28.6 (1849)	...
University	26.5 (272)	22.5 (1457)	...
Physical activity, % (n)			< .001
Inactive	8.8 (90)	5.5 (670)	...
Moderately inactive	35.0 (357)	32.4 (3914)	...
Moderately active	42.4 (432)	49.0 (5924)	...
Very active	13.7 (140)	13.1 (1582)	...
Blood pressure			
Hypertension, yes, % (n)	43.9 (451)	57.9 (6953)	< .001
Antihypertensive treatment, yes, % (n)	17.0 (171)	15.4 (1834)	.192
Systolic blood pressure, mm Hg, median (IQR)	129 (119–141)	138 (127–152)	< .001
Diastolic blood pressure, mm Hg, median (IQR)	79 (73–87)	85 (78–93)	< .001
Lipids			
Elevated LDL-C, yes, % (n)	24.0 (229)	22.7 (2649)	.358
Hypertriglyceridemia, yes, % (n)	48.7 (478)	38.2 (4494)	< .001
Antidyslipidemic treatment, yes, % (n)	14.0 (142)	10.6 (1266)	.001
LDL-C, mmol/L, median (IQR)	2.7 (2.2–3.4)	3.0 (2.4–3.6)	< .001
Triglycerides, mmol/L, median (IQR)	1.7 (1.2–2.7)	1.5 (1.0–2.5)	< .001
Glucose metabolism			
Antidiabetic treatment, yes, % (n)	3.2 (32)	3.0 (358)	.811
Glycated hemoglobin, mmol/mol, median, (IQR)	34.0 (31.7–36.6)	35.1 (33.0–37.4)	< .001
Glucose, mmol/L, median (IQR)	5.0 (4.5–5.5)	5.0 (4.6–5.5)	.109
Abdominal obesity, yes, % (n)	63.5 (674)	59.8 (7236)	.018
Waist circumference, cm, median (IQR)	93 (86–102)	93 (85–101)	.143
Hip circumference, cm, median (IQR)	101 (96–106)	102 (98–107)	< .001
Metabolic syndrome, yes, % (n)	37.8 (338)	35.0 (4024)	.092
High-sensitivity CRP, mg/dl, median (IQR)	1.2 (0.6–2.5)	1.0 (0.5–1.9)	< .001
BMI, median (IQR)	24.6 (22.4–27.1)	26.0 (23.8–28.7)	< .001
BMI World Health Organization categories, % (n)			< .001
Underweight, <18.5	2.7 (29)	0.5 (56)	...
Normoweight, 18.5–24.9	52.8 (576)	37.7 (4569)	...
Overweight, 25–29.9	34.8 (380)	44.9 (5444)	...
Obese, ≥30	9.7 (160)	16.9 (2050)	...

In exploratory analysis, metabolic syndrome was defined as a minimum of 3 of the following 5: waist circumference ≥94 cm in men and ≥80 cm in women; systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg and/or antihypertensive treatment; nonfasting plasma triglyceride ≥1.693 mmol/L; high-density lipoprotein cholesterol ≤1.036 mmol/L in men and ≤1.295 mmol/L in women; self-reported diabetes and/or antidiabetic treatment and/or plasma glucose ≥11.1 mmol/L [18].

Abbreviations: BMI, body mass index; CRP, C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol.

As sensitivity analyses, the associations between HIV infection and abdominal obesity and elevated LDL-C, respectively, were explored in multivariable logistic regression models

stratified both by present/previous didanosine (ddI)/stavudine (d4T)/zidovudine (AZT) exposure (yes vs no) and cART initiation date (before and after 2005), separately. This arbitrary

and a priori–defined cutoff aims to represent the time point for the shift to newer antiretroviral regimens characterized by fewer metabolic side effects. As an additional sensitivity analysis, when testing the association between HIV infection and hypertension, logistic regression analyses were performed using all COCOMO participants and 3 randomly selected CGPS participants for every PLWH, matched using gender and 5-year age strata, thus eliminating sex and age differences between the 2 groups (Supplementary Table 1). As an exploratory analysis, the association between HIV infection and the presence of metabolic syndrome was analyzed. Finally, in order to evaluate the possible impact of a lower threshold when defining elevated LDL-C, the association between HIV infection and elevated LDL-C was also tested using ≥ 3.00 mmol/L as the cutoff [21]. In all sensitivity analyses, the same covariates as in the primary analyses were included in the models.

Interaction between age and HIV status was tested in multivariable logistic analysis models, with abdominal obesity, elevated LDL-C, hypertriglyceridemia, and hypertension as dependent variables. In these analyses, age was grouped into quartiles. A *P* value < .05 was considered statistically significant. Analyses were conducted using R (V.3.3.0).

RESULTS

Demographics

A total of 1099 COCOMO and 12 161 CGPS participants were included. Characteristics of the participants are shown in

Table 2. Human Immunodeficiency Virus (HIV)-Specific Variables for People Living With HIV Included in the Study

Characteristic	People Living With Human Immunodeficiency Virus, n = 1099
Transmission mode, % (n)	
Heterosexual	21.6 (235)
Intravenous drug use	1.5 (16)
Male-to-male sex	71.2 (775)
Other	5.8 (63)
Current CD4, median (IQR)	690 (520–890)
Current CD4 group, % (n)	
<200	1.8 (20)
200–349	5.5 (60)
350–500	15.2 (165)
>500	77.5 (842)
CD4 nadir <200, % (n)	42.0 (450)
CD4/CD8 ratio, median (IQR)	0.8 (0.6–1.1)
cART, yes, % (n)	98.4 (1078)
Current viral load <50, % (n)	94.7 (1030)
Years since human immunodeficiency virus infection, median (IQR)	13.7 (6.9–21.3)
Years since cART initiation, median (IQR)	10.5 (5.2, 17.3)
Hepatitis C virus-RNA, yes, % (n)	5.3 (58)

Abbreviations: cART, combined antiretroviral therapy; IQR, interquartile range.

Table 1. HIV-specific characteristics of COCOMO participants are shown in Table 2.

Abdominal Obesity in PLWH and Uninfected Controls

PLWH had lower BMI compared to uninfected controls (Table 1). In contrast, PLWH had higher prevalence of abdominal obesity (63.5% vs 59.8%, *P* value .018; Table 1). In logistic regression analyses, HIV infection was associated with the presence of abdominal obesity (OR, 1.17 [1.03–1.34] and aOR, 1.92 [1.60–2.30]; Table 3). This result was reproduced when all controls and PLWH who initiated cART before 2005 were included (*n* = 514; aOR, 2.84 [2.18–3.73]) and when all controls and PLWH who started cART after 2005 were included (*n* = 544; aOR, 1.28 [1.01–1.72]; Supplementary Figure 1). Comparable results were obtained when PLWH were stratified according to ddI/d4T/AZT exposure (Supplementary Table 2).

The association between abdominal obesity and HIV increased as persons aged (*P* < .0001, test for interaction), from an aOR of 1.46 (1.06–2.00) in those aged 20–45 years to 2.75 (1.75–4.73) in those aged 60–89 years. A plot representing this interaction is shown in Figure 1.

Abdominal obesity was associated with elevated LDL-C, hypertriglyceridemia, and hypertension in uni- and multivariable logistic regression analyses (Table 3).

Elevated LDL-C, Hypertriglyceridemia, and Hypertension in PLWH and Uninfected Controls

PLWH had lower LDL-C but higher prevalence of current lipid-lowering treatment compared to uninfected controls (Table 1). No difference was found in prevalence of elevated LDL-C (24.0% vs 22.7%, *P* value .358; Table 1). HIV infection was associated with elevated LDL-C in multivariable analysis (aOR, 1.32 [1.09–1.59]) only after adjusting for BMI (Table 3). Furthermore, time of initiation of cART had an effect on the association between HIV infection and elevated LDL-C (cART initiation before 2005, aOR, 1.74 [1.37–2.19] and cART initiation after 2005, aOR, 0.80 [0.58–1.09]). Comparable results were found when PLWH were stratified according to ddI/d4T/AZT exposure (Supplementary Table 2). No association between HIV infection and elevated LDL-C was found when this outcome was defined as LDL ≥ 3.00 mmol/L (OR, 0.87 [0.74–1.02]).

The association between HIV infection and elevated LDL-C was different in younger and older persons (*p* interaction 0.033). While there was no significant association between HIV and elevated LDL-C in those aged 20–52 years, a positive association was found in persons aged 52–60 (aOR, 1.66 [1.16–2.38]) and 60–89 (aOR, 1.32 [0.94–1.84]) without, however, reaching statistical significance in the latter.

PLWH had lower systolic blood pressure and lower diastolic blood pressure compared to uninfected controls, and no difference in prevalence of current antihypertensive treatment was

Table 3. Human Immunodeficiency Virus Infection as Independent Risk Factor for Abdominal Obesity, Elevated Low-Density Lipoprotein Cholesterol, Hypertriglyceridemia, and Hypertension

Covariates	Abdominal Obesity		Elevated Low-Density Lipoprotein Cholesterol		Hypertriglyceridemia		Hypertension	
	Unadjusted OR (95% CI)	aOR (95% CI)	Unadjusted OR (95% CI)	aOR (95% CI)	Unadjusted OR (95% CI)	aOR (95% CI)	Unadjusted OR (95% CI)	aOR (95% CI)
Human immunodeficiency virus, yes vs no	1.17 ^a [1.03–1.34]	1.92 ^a [1.60–2.30]	1.08 [0.92–1.26]	1.32 ^b [1.09–1.59]	1.53 ^a [1.35–1.75]	1.76 ^a [1.49–2.08]	0.57 ^a [0.50–0.65]	0.63 ^a [0.54–0.74]
Sex, male vs female	3.50 ^a [3.19–3.84]	3.37 ^a [2.88–3.95]	1.94 ^a [1.72–2.20]	1.40 ^a [1.16–1.69]	3.34 ^a [2.99–3.74]	2.45 ^a [2.08–2.90]	2.50 ^a [2.28–2.74]	2.21 ^a [1.84–2.45]
Age, per 5 years	1.92 ^a [1.85–1.99]	1.79 ^a [1.69–1.90]	1.32 ^a [1.29–1.35]	1.27 ^a [1.23–1.31]	1.19 ^a [1.17–1.21]	1.10 ^a [1.07–1.13]	1.35 ^a [1.33–1.38]	1.30 ^a [1.27–1.34]
Abdominal obesity, yes vs no	3.00 ^a [2.73–3.32]	1.44 ^a [1.23–1.69]	4.51 ^a [4.15–4.90]	2.12 ^a [1.86–2.41]	2.84 ^a [2.64–3.06]	1.32 ^a [1.16–1.49]

Multivariable models have been adjusted for human immunodeficiency virus infection, sex, age, body mass index, physical activity, origin, education level, abdominal obesity (except when abdominal obesity was used as dependent variable), and smoking status.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.

P values significance: ^a, <.001; ^b, <.01.

found (Table 1). PLWH had lower prevalence of hypertension compared to uninfected controls (43.9% vs 57.9%, $P < .001$), and a negative association was found between HIV infection and the presence of hypertension (OR, 0.57 [0.50–0.65] and aOR, 0.63 [0.54–0.74]; Table 3). These results were reproduced in sensitivity analyses using 3 age- and gender-matched uninfected controls for every COCOMO participant in order to achieve a perfect sex and age matching (aOR, 0.70 [0.57–0.87]).

PLWH had a higher concentration of triglycerides and a higher prevalence of hypertriglyceridemia compared to uninfected controls (Table 1). HIV infection was associated with higher risk of hypertriglyceridemia (OR, 1.53 [1.35–1.75] and aOR, 1.76 [1.49–2.08]). The association between HIV status and both hypertension and hypertriglyceridemia was similar across different age groups (p interaction 0.39 and 0.09, respectively).

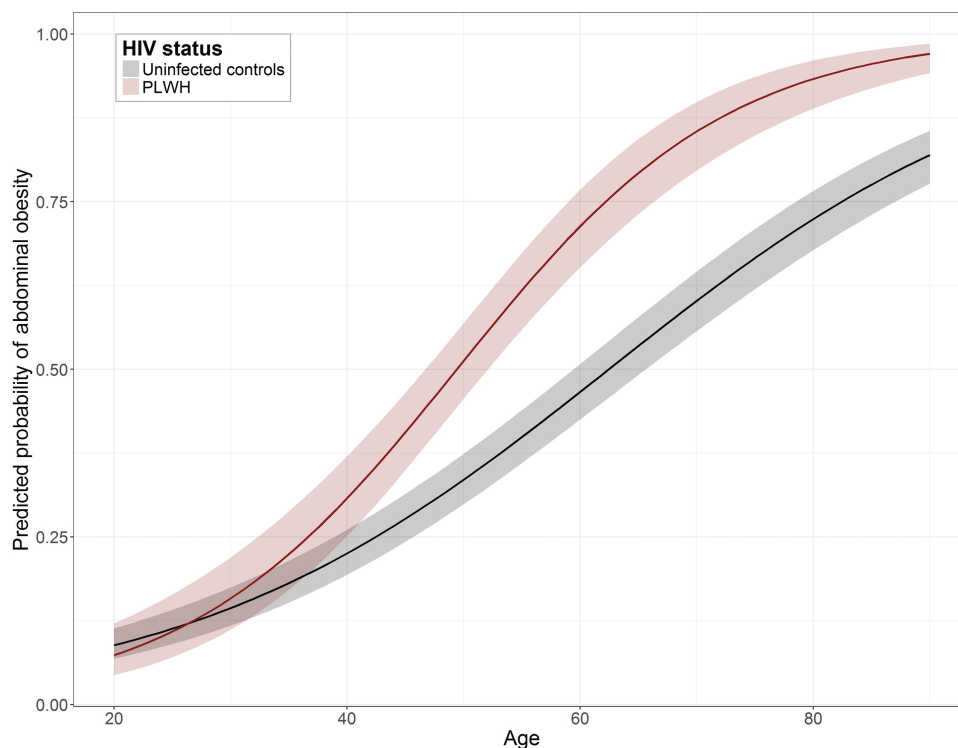


Figure 1. Predicted probability of abdominal obesity according to age in normoweight uninfected controls and people living with human immunodeficiency virus (PLWH). Predicted probabilities for the presence of abdominal obesity in normoweight PLWH and controls were calculated using a logistic regression model that included an interaction term between human immunodeficiency virus (HIV) infection and age, age, body mass index = 22, sex = "male," origin = "Scandinavian," smoking status = "former smoker," physical activity = "moderately active," and education level = "vocational." Abbreviation: HIV, human immunodeficiency virus.

In exploratory analysis, HIV infection was associated with increased risk of metabolic syndrome (OR, 1.68 [1.39–2.03]).

HIV-Related Predictors of Abdominal Obesity, Elevated LDL-C, Hypertriglyceridemia, and Hypertension

Low CD4 nadir and duration of HIV infection were associated with the presence of abdominal obesity (aOR, 1.71 [1.12–2.62] and aOR, 1.37 per 5 years [1.11–1.70], respectively; Figure 2).

Low CD4 nadir and duration of cART were positively associated with the presence of elevated LDL-C (aOR, 1.67 [1.09–2.55] and aOR, 1.56 per 5 years [1.17–2.09]) and hypertension (aOR, 1.60 [1.10–2.34] and aOR, 1.29 per 5 years [1.00–1.66], respectively; Figure 2).

Duration of cART was associated with the presence of hypertriglyceridemia (aOR, 1.32 per 5 years [1.04–1.70]).

DISCUSSION

The redistribution of body fat toward the abdomen is associated with increased risk of CVD in PLWH [24] and was classically described as a serious, yet obsolete complication of HIV infection due to its association with old-generation cART [10]. In this study, we found that abdominal obesity remains a distinct HIV-related phenotype, in particular, among older PLWH. Furthermore, abdominal obesity was associated with elevated LDL-C, hypertriglyceridemia, and hypertension. Our results suggest a link between HIV and proatrogenic metabolic factors, partly mediated by abdominal obesity.

CVD is the leading contributor to non-AIDS morbidity and mortality in PLWH [4]. The mechanisms behind the increased risk of CVD in PLWH, however, have not been fully elucidated. The fat redistribution syndrome that characterized the early stages of HIV epidemic [8] was a serious complication of old-generation antiretroviral treatments due to its association with CVD risk factors [24]. After the introduction of cART with minor metabolic side effects, the incidence of fat redistribution syndrome among PLWH declined [10, 25] and so has the attention toward this condition. In this study, however, PLWH had higher prevalence of abdominal obesity compared to uninfected controls, despite having lower BMI. Furthermore, HIV infection was associated with increased risk of abdominal obesity, also after stratifying PLWH according to cART initiation date (pre- and post-2005). These results suggest that either HIV per se or modern cART may contribute to fat redistribution syndrome as this remains a problem even in contemporary treated PLWH. However, higher risk of abdominal obesity observed in PLWH with initiation of cART prior to 2005 supports a more harmful effect of old-generation cART on abdominal fat distribution compared to newer regimens.

Interestingly, for a given BMI, the association between HIV infection and abdominal obesity was exacerbated by age. Aging is known to cause fat tissue redistribution from subcutaneous to intraabdominal compartments [26]. This is mainly due to systemic inflammation and dysdifferentiation of preadipocytes into a proinflammatory, senescent-like and tissue-remodeling

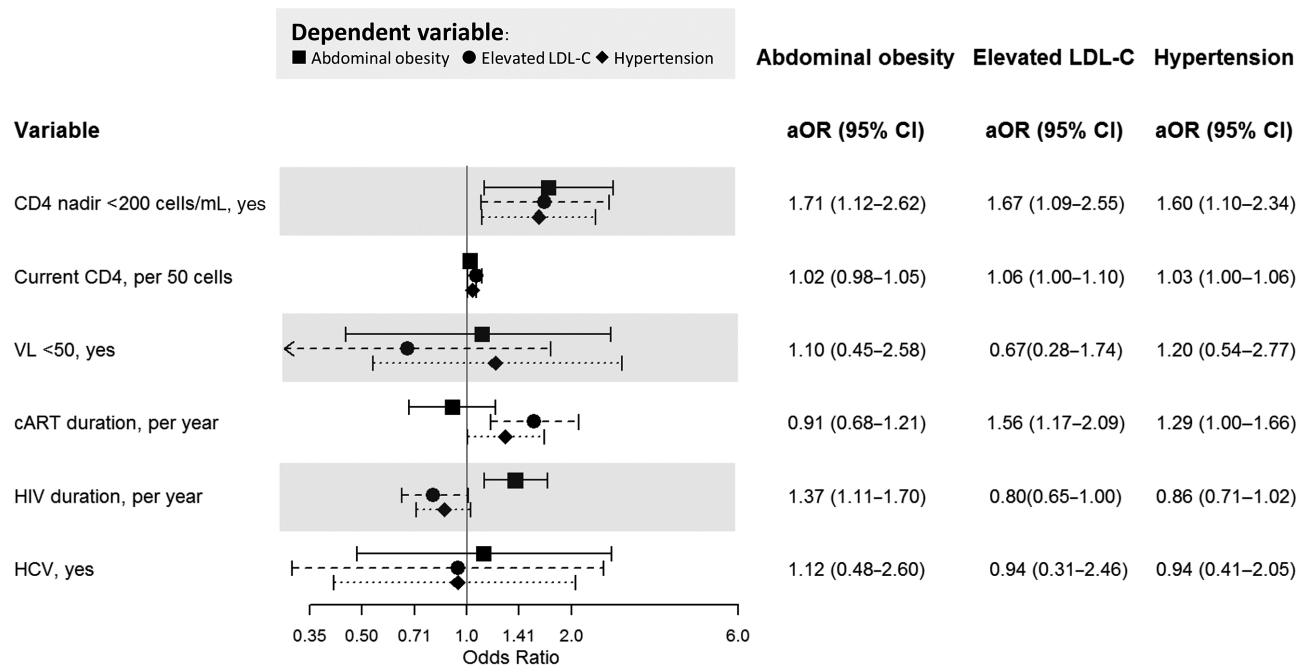


Figure 2. Human immunodeficiency virus (HIV)-specific predictors for abdominal obesity, elevated low-density lipoprotein cholesterol (LDL-C), and hypertension. Adjusted odds ratios from multivariable logistic regression analyses with abdominal obesity, elevated LDL-C, and hypertension as dependent variables, respectively. All the models were adjusted for age, gender, smoking history, physical activity, origin, education, abdominal obesity (except when using abdominal obesity as dependent variable), body mass index, current CD4, CD4 nadir, current viral load, time since HIV infection, time since combination antiretroviral therapy initiation, and hepatitis C virus coinfection. Abbreviations: aOR, adjusted odds ratio; cART, combined antiretroviral therapy; CI, confidence interval; HCV, hepatitis C virus; VL, viral load.

state, which leads to an imbalance between lipolysis and lipogenesis [27]. A similar cascade of events is described in HIV-associated fat redistribution syndrome [28], where both host and HIV-specific factors are involved [12, 28]. In accordance with previous literature [29], we described associations between low CD4 nadir, duration of HIV infection, and the presence of abdominal obesity. Low CD4 nadir may be considered an indirect measure of the length of ongoing viral replication [30]. A prolonged exposure to viral proteins may interfere directly with lipogenesis by inhibiting PPAR-gamma receptor activity in adipocytes [12]. We hypothesize that age- and HIV-associated fat redistribution syndromes are characterized by parallel yet interconnected pathways that amplify each other, leading to a synergistic interaction between aging and HIV infection causing abdominal obesity in PLWH. This interaction, together with the association found between abdominal obesity and elevated LDL-C, hypertriglyceridemia, and hypertension, may partly explain the increased risk of premature CVD in PLWH [31].

Dyslipidemia has been described to be associated with increased risk of CVD in PLWH [3]. Consistent with previous literature [3], we found that HIV infection was associated with higher risk of hypertriglyceridemia and, after adjusting for BMI, elevated LDL-C. However, when only PLWH who initiate treatment after 2005 were considered, no evidence of association between HIV infection and elevated LDL-C was found. Although power for this analysis was lower than in primary analyses, this result may be due to the exposure to different antiretroviral regimes introduced prior to and after 2005, the latter being characterized by fewer metabolic side effects compared to older-generation cART. While having declined in the last decade [25], the prevalence of lipid metabolism disturbances and abdominal obesity still remains high in PLWH and warrants continued attention.

Hypertension is a major CVD risk factor [32], and the possible association between HIV infection and hypertension has been widely studied, with contradictory results [5, 33–38]. PLWH have been described to have lower [33, 34], comparable [35, 36], and higher [5, 37, 38] prevalence of hypertension compared to uninfected controls. In contrast to our predefined hypothesis, we found that PLWH had lower prevalence of hypertension and that HIV infection was associated with lower risk of hypertension, even in the sensitivity analysis performed. Of note, the prevalence of hypertension in CGPS participants was high (57.9%), as described in previous studies [14, 19], yet comparable to other Danish general population studies [39]. Due to the size of cohorts included in this study and the overlapping recruitment area between the 2 groups, we do not believe that sample size or geographical differences explain the findings. There is no obvious biological mechanism that could explain why HIV infection should protect against hypertension, and we suggest that the association found between HIV infection and low risk of hypertension may be due to confounding factors we were not able to account for. It is worth noticing that this finding was mainly driven by undiagnosed and

thus untreated hypertension, which may represent a more pronounced white-coat effect in the uninfected population, which is less exposed to the hospital environment compared to PLWH.

HIV was associated with increased odds of abdominal obesity, which was associated with elevated LDL, hypertriglyceridemia, and hypertension. In turn, HIV was associated with increased odds for both elevated LDL and hypertriglyceridemia. As discussed above, PLWH had lower odds of hypertension. In contrast with the direct and detrimental impact that HIV per se and cART have been described to have on both fat tissue and lipid metabolism [28], the effect of HIV on hypertension may be predominantly indirect, mediated by several factors including abdominal obesity, which may result in weaker associations.

The main limitation to the present study is that PLWH and uninfected controls were included from 2 centers, University of Copenhagen–Rigshospitalet and University of Copenhagen–Herlev Hospital, respectively. The use of different equipment at the 2 sites may have led to minor methodologic differences that we were not able to account for. However, the same model of equipment was used in both centers, and all the investigations were performed by trained medical staff following identical protocols. Minor differences in age and gender found between the 2 populations may explain part of the differences in the prevalence of the outcomes. However, a possible confounding effect of these variables was reduced by adjusting for, among the others, age and gender in multivariable analyses.

To our knowledge, this is the largest study to report data regarding abdominal obesity, elevated LDL-C, hypertriglyceridemia, and hypertension in PLWH and uninfected controls. Adjusting for lifestyle and demographic factors, we were able to investigate the effect of HIV infection and to reduce the effect of possible confounders.

In conclusion, our study suggests that abnormal fat distribution and abdominal obesity remain prominent features of contemporarily treated PLWH and may contribute to continued excess risk of premature CVD in this population, given both the deleterious interaction found between HIV infection and aging in causing abdominal obesity and its association with elevated LDL-C, hypertriglyceridemia, and hypertension. Renewed attention by the medical community toward the abdominal obesity phenotype and innovative interventions that target this condition are therefore needed in order to reduce the risk of CVD in PLWH.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. We thank all the study participants for their involvement. We thank the staff at the Department of Infectious Diseases at Rigshospitalet and Hvidovre Hospital for their dedicated participation.

Disclaimer. The study was designed, conducted, analyzed, and written by the authors without involvement of any commercial party.

Financial support. This work was supported by the Rigshospitalet Research Council, Region Hovedstaden, the Lundbeck Foundation, the Novo Nordisk Foundation, and the Danish National Research Foundation (grant 126).

Potential conflicts of interest. A. N. R.: travel grants from Gilead. A. M.: honoraria, lecture fees, and travel support from BMS, BI, Pfizer, Merck, ViiV, and Wragge LLC. J. G.: honoraria for consulting and presenting paid to his institution from Gilead, Abbvie, ViiV, BMS, MSD, Janssen, and Medivir. A. M. L.: travel grants from Gilead and GSK. S. D. N.: unrestricted research grants from Novo Nordisk Foundation, Lundbeck Foundation, Augustinus Foundation, Rigshospitalet Research Council; travel grants from Gilead, MSD, BMS, and GSK/ViiV; and advisory board activity for Gilead and GSK/ViiV. All remaining authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

- van Sighem AI, Gras LA, Reiss P, Brinkman K, de Wolf F; ATHENA National Observational Cohort Study. Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals. *AIDS* **2010**; *24*:1527–35.
- Legarth RA, Ahlström MG, Kronborg G, et al. Long-term mortality in HIV-infected individuals 50 years or older: a nationwide, population-based cohort study. *J Acquir Immune Defic Syndr* **2016**; *71*:213–8.
- Petoumenos K, Reiss P, Ryom L, et al; D:A:D Study Group. Increased risk of cardiovascular disease (CVD) with age in HIV-positive men: a comparison of the D:A:D CVD risk equation and general population CVD risk equations. *HIV Med* **2014**; *15*:595–603.
- Sackoff JE, Hanna DB, Pfeiffer MR, Torian LV. Causes of death among persons with AIDS in the era of highly active antiretroviral therapy: New York City. *Ann Intern Med* **2006**; *145*:397–406.
- van Zoest RA, Wit FW, Kooij KW, et al; AGEHIV Cohort Study Group. Higher prevalence of hypertension in HIV-1-infected patients on combination antiretroviral therapy is associated with changes in body composition and prior stavudine exposure. *Clin Infect Dis* **2016**; *63*:205–13.
- Lake JE, Wohl D, Scherzer R, et al. Regional fat deposition and cardiovascular risk in HIV infection: the FRAM study. *AIDS Care* **2011**; *23*:929–38.
- Jacobson DL, Knox T, Spiegelman D, Skinner S, Gorbach S, Wanke C. Prevalence of, evolution of, and risk factors for fat atrophy and fat deposition in a cohort of HIV-infected men and women. *Clin Infect Dis* **2005**; *40*:1837–45.
- Carr A, Samaras K, Burton S, et al. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. *AIDS* **1998**; *12*:F51–8.
- Hadigan C, Meigs JB, Corcoran C, et al. Metabolic abnormalities and cardiovascular disease risk factors in adults with human immunodeficiency virus infection and lipodystrophy. *Clin Infect Dis* **2001**; *32*:130–9.
- Srinivasa S, Grinspoon SK. Metabolic and body composition effects of newer antiretrovirals in HIV-infected patients. *Eur J Endocrinol* **2014**; *170*:R185–202.
- Vidal F, Gutiérrez F, Gutiérrez M, et al. Pharmacogenetics of adverse effects due to antiretroviral drugs. *AIDS Rev* **2010**; *12*:15–30.
- Villarroya F, Domingo P, Giral M. Lipodystrophy in HIV 1-infected patients: lessons for obesity research. *Int J Obes (Lond)* **2007**; *31*:1763–76.
- 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* **2016**; *16*:713.
- Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. *JAMA* **2007**; *298*:299–308.
- Vedel-Krogh S, Nielsen SF, Lange P, Vestbo J, Nordestgaard BG. Blood eosinophils and exacerbations in chronic obstructive pulmonary disease: The Copenhagen General Population Study. *Am J Respir Crit Care Med* **2016**; *193*:965–74.
- Afzal S, Tybjaerg-Hansen A, Jensen GB, Nordestgaard BG. Change in body mass index associated with lowest mortality in Denmark, 1976–2013. *JAMA* **2016**; *315*:1989–96.
- Thomsen M, Nordestgaard BG. Myocardial infarction and ischemic heart disease in overweight and obesity with and without metabolic syndrome. *JAMA Intern Med* **2014**; *174*:15–22.
- World Health Organization. Waist circumference and waist-hip ratio: report of a WHO expert consultation. *World Heal Organ* **2008**:8–11.
- Timpson NJ, Harbord R, Davey Smith G, Zacho J, Tybjaerg-Hansen A, Nordestgaard BG. Does greater adiposity increase blood pressure and hypertension risk?: Mendelian randomization using the FTO/MC4R genotype. *Hypertens (Dallas, Tex. 1979)* **2009**; *54*:84–90.
- Stone NJ, Robinson JG, Lichtenstein AH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 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. *Circulation* **2014**; *129*:S1–45.
- Nordestgaard BG, Langsted A, Mora S, et al; European Atherosclerosis Society and the European Federation of Clinical Chemistry and Laboratory Medicine Joint Consensus Initiative. Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points—a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. *Eur Heart J* **2016**; *37*:1944–58.
- James PA, Oparil S, Carter BL, et al. 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* **2014**; *311*:507–20.
- Alberti KG, Eckel RH, Grundy SM, et al; International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* **2009**; *120*:1640–5.
- Hadigan C, Meigs JB, Corcoran C, et al. Metabolic abnormalities and cardiovascular disease risk factors in adults with human immunodeficiency virus infection and lipodystrophy. *Clin Infect Dis* **2001**; *32*:130–9.
- Price J, Hoy J, Ridley E, Nyulasi I, Paul E, Woolley I. Changes in the prevalence of lipodystrophy, metabolic syndrome and cardiovascular disease risk in HIV-infected men. *Sex Health* **2015**; *12*:240–8.
- Kuk JL, Saunders TJ, Davidson LE, Ross R. Age-related changes in total and regional fat distribution. *Ageing Res Rev* **2009**; *8*:339–48.
- Martyniak K, Masternak MM. Changes in adipose tissue cellular composition during obesity and aging as a cause of metabolic dysregulation. *Exp Gerontol* **2017**; *94*:59–63.
- Caron-Debarle M, Lagathu C, Boccara F, Vigouroux C, Capeau J. HIV-associated lipodystrophy: from fat injury to premature aging. *Trends Mol Med* **2010**; *16*:218–29.
- Mauss S, Corzilius M, Wolf E, et al; DAGNA Lipantiretroviral Therapy Study Group. Risk factors for the HIV-associated lipodystrophy syndrome in a closed cohort of patients after 3 years of antiretroviral treatment. *HIV Med* **2002**; *3*:49–55.
- Hunt PW, Martin JN, Sinclair E, et al. T cell activation is associated with lower CD4+ T cell gains in human immunodeficiency virus-infected patients with sustained viral suppression during antiretroviral therapy. *J Infect Dis* **2003**; *187*:1534–43.
- Guaraldi G, Orlando G, Zona S, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. *Clin Infect Dis* **2011**; *53*:1120–6.
- Nauta ST, Deckers JW, van der Boon RM, Akkerhuis KM, van Domburg RT. Risk factors for coronary heart disease and survival after myocardial infarction. *Eur J Prev Cardiol* **2014**; *21*:576–83.
- Kwarisiima D, Balzer L, Heller D, et al. Population-based assessment of hypertension epidemiology and risk factors among HIV-positive and general populations in rural Uganda. *PLoS One* **2016**; *11*:e0156309.
- Savès M, Chêne G, Ducimetière P, et al; French WHO MONICA Project and the APROCO (ANRS EP11) Study Group. Risk factors for coronary heart disease in patients treated for human immunodeficiency virus infection compared with the general population. *Clin Infect Dis* **2003**; *37*:292–8.
- Bergersen BM, Sandvik L, Dunlop O, Birkeland K, Bruun JN. Prevalence of hypertension in HIV-positive patients on highly active retroviral therapy (HAART) compared with HAART-naïve and HIV-negative controls: results from a Norwegian study of 721 patients. *Eur J Clin Microbiol Infect Dis* **2003**; *22*:731–6.
- Baekken M, Os I, Sandvik L, Oektedalen O. Hypertension in an urban HIV-positive population compared with the general population: influence of combination antiretroviral therapy. *J Hypertens* **2008**; *26*:2126–33.
- Hasse B, Tarr PE, Marques-Vidal P, et al. Strong impact of smoking on multimorbidity and cardiovascular risk among human immunodeficiency virus-infected individuals in comparison with the general population. *Open Forum Infect Dis* **2015**; *2*:ofv108.
- Gazzaruso C, Bruno R, Garzaniti A, et al. Hypertension among HIV patients: prevalence and relationships to insulin resistance and metabolic syndrome. *J Hypertens* **2003**; *21*:1377–82.
- Bergholdt HK, Bathum L, Kvetny J, et al. Study design, participation and characteristics of the Danish General Suburban Population Study. *Dan Med J* **2013**; *60*:A4693.