Cardiovascular disease and diabetes in HIV-positive and -negative gay and bisexual men over the age of 55 years in Australia: insights from the Australian Positive & Peers Longevity Evaluation Study (APPLES)

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Abstract

Objectives

As HIV-positive people age, diagnosis and management of comorbidities associated with ageing are of increasing concern. In this study we aimed to compare the self-reported prevalence of heart disease, stroke, thrombosis, and diabetes in older Australian HIV-positive and HIV-negative gay and bisexual men (GBM).

Methods

We analysed data from the Australian Positive & Peers Longevity Evaluation Study (APPLES), a prospectively recruited cross-sectional sample of 228 (51.1%) HIV-positive and 218 (48.9%) HIV-negative GBM, aged ≥ 55 years. Regression methods were used to assess the association of HIV status with self-reported comorbidities.

Results

Of 446 patients, 389 (200 [51.4%] HIV-positive) reported their disease history. The reported prevalence of comorbidities was higher in the HIV-positive group: heart disease 19.5% vs. 12.2%; stroke 7.5% vs. 4.2%; thrombosis 10.5% vs. 4.2%; and diabetes 15.0% vs. 9.0%. In adjusted analyses HIV-positive GBM had significantly increased odds of reporting heart disease (adjusted odds ratio (aOR) 1.99, $p=0.03$) and thrombosis (aOR 2.87, $p=0.01$). In our analysis, HIV status was not significantly associated with either age at diagnosis of heart disease (median 53 for HIV-positive vs. 55 for HIV-negative GBM, $p=0.64$) or 5-year CVD risk estimated by using the Framingham Risk Score.

Conclusions

HIV-positive GBM more commonly reported heart disease and thrombosis compared to their HIV-negative peers. These results further highlight the need to understand the impact of HIV on age-related comorbidities in GBM, to guide optimal screening and treatment strategies to reduce the risk of these comorbidities among the HIV-positive population.

Introduction

As the HIV epidemic has matured in Australia an increasing proportion of those living with HIV are aged over 50 years. Thus, diagnosis and management of comorbidities associated with ageing, including cardiovascular disease (CVD) and diabetes mellitus (DM), have become of increasing importance in the long-term management of these patients. Among other factors, it has long been debated whether the increased prevalence of such comorbidities in the HIV-positive population, compared to the HIV-negative population, is a possible result of premature ageing (1-5). While conditions such as persistent chronic inflammation, immune depletion and increased multimorbidity (5-8) suggest an accelerated immunosenescence among people with HIV, the effects on onset of end-organ specific diseases, including CVD and DM, remain less clear with evidence tending to support higher prevalence of some disease at any age rather than earlier occurrence (3, 4).

In the general Australian adult population, approximately 4.2 million people (22%) had CVD in 2014-15 (9). Over the past three decades, the prevalence of diabetes has more than doubled, with an estimated 1.2 million adults (6%) living with diabetes in 2014-2015 (10). In both cases, a large proportion of this burden is being experienced by older people (9, 10). In Australia, 43% of HIV-positive people are now over 50 years of age and are predominately gay and bisexual men (GBM) (11). Along with traditional risk factors, both HIV infection itself and the use of certain antiretrovirals have been independently associated with an increased risk of CVD (12-15). Furthermore, HIV infection and its treatment are associated with well described CVD risk factors such as higher total and low-density lipoprotein (LDL) cholesterol and lower high-density lipoprotein (HDL) cholesterol, lipodystrophy, and the metabolic syndrome (16).

DM is a leading cause of CVD among people living with HIV; data from the D:A:D study suggest that the risk of myocardial infarction is more than doubled among HIV-positive patients with diabetes (12). While cumulative exposure to some nucleoside analogue reverse transcriptase inhibitors (NRTI) and protease inhibitors (PI), particularly stavudine, zidovudine, didanosine, indinavir and saquinavir, is associated with incident DM (17-21), there is conflicting evidence on whether HIV infection itself is an independent risk factor for DM (20). Certainly, some factors that influence DM incidence in the general population are more common in HIV-positive patients such as hepatitis C virus infection or the use of certain medications including atypical antipsychotics, and corticosteroids (20).

With very few published data from well-matched studies, the objective of this analysis was to compare known and potential risk factors of CVD and DM, as well as effects of ageing, in HIV-positive GBM over the age of 55 years in Australia with a comparable HIV-negative control group. This is of great importance to guide optimal screening and treatment strategies to reduce the harm associated with these comorbidities among the ageing HIV-positive population.

Methods

Patient selection

These analyses are based on data from the Australian Positive & Peers Longevity Evaluation Study (APPLES). The methods of APPLES have previously been described in detail (6). In brief, APPLES was a prospectively recruited cross-sectional sample of HIV-positive and HIV-negative persons who identify as GBM, aged 55 years and over. Recruitment to APPLES commenced in August 2014, with a recruitment target of 450 (225 HIV-positive and 225 HIV-negative) GBM. HIV-negative men were required to have had a negative HIV antibody test within the last 12 months. The study consisted of two parts: clinical data recorded at the recruiting sites and a self-completed health and lifestyle questionnaire. All participants were tested for biomarkers of systemic inflammation, coagulation and impaired renal function: interleukin 6 (IL-6), D-dimer, high-sensitivity C-reactive protein (hsCRP),

and cystatin C. Participants were eligible for this current analysis if they answered the APPLES questionnaire.

The main outcome variables, heart disease, stroke, thrombosis, and diabetes, were based on answers to the self-reported question '*Has your doctor EVER told you that you have...*'; additionally, diabetes as a risk factor was reported present if a participant currently received either insulin or oral hypoglycaemic medication. Family history of a disease was defined as either parent having had the disease. The 5-year cardiovascular risk was estimated with the Framingham Risk Score (22) and the D:A:D reduced model (23).

Ethics approval was obtained from all relevant institutional review boards and the St Vincent's Hospital Human Research Ethics Committee and other relevant HRECs as appropriate, and written informed consent was obtained from all participants.

Statistical analysis

The study groups were compared using Pearson's χ^2 -test, Fisher's exact test and the Wilcoxon rank sum test as appropriate. Logistic regression methods were used to assess the effect of HIV status on the self-reported comorbidities heart disease, stroke, thrombosis, and diabetes. In multivariate analyses, stepwise backward selection of covariates, with a significance level of 0.05 for removal, was used to develop multivariate models. All models were adjusted *a priori* for the established risk factors of age, smoking and family history of the respective disease, all considered to be independent of HIV infection. As the aim was to analyse the impact of HIV infection on the outcome variables, HIV status was also included *a priori* in all models. Furthermore, we excluded number of medications reported as being currently taken by participants from the multivariate analyses due to a strong correlation with HIV status. Due to the design of the study, the association of laboratory values and biomarkers with the primary outcomes could not be tested.

For the CVD risk analyses, we excluded participants who reported ever having had heart disease. We looked at differences in mean risk by applying linear regression models. Again, to account for non-HIV related factors, we adjusted *a priori* for age and smoking.

Sensitivity analysis was performed excluding any diseases prior to the age of 16 and prior to participants' HIV diagnosis.

Statistical significance was assessed at the α -level=0.05. All analyses were conducted using SAS/STAT software, Version 9.4 of the SAS system for Windows (SAS Institute, Cary NC) and R Version 3.4.2(24).

Results

Between August 2014 and December 2015, 228 HIV-positive participants and 218 HIV-negative controls completed a baseline visit. After the exclusion of participants with missing questionnaires, we identified 200 (87.7% of total) HIV-positive and 189 (86.7% of total) HIV-negative participants to be eligible for this analysis.

Compared with HIV-positive participants, HIV-negative participants were older, had a higher BMI, higher levels of LDL and total cholesterol, but less commonly reported ever smoking cigarettes (**Table 1**). Of all participants, 62 (15.9%) reported ever having heart disease, 23 (5.9%) stroke, 29 (7.5%) thrombosis, and 47 (12.1%) diabetes. Crude rates of all reported comorbidities were higher in the HIV-positive group and significantly so for both heart disease and thrombosis **Table 1**).

After adjustment, HIV infection was associated with having ever had heart disease (adjusted odds ratio [aOR] 1.99 [confidence interval (CI) 1.09-3.65], $p=0.025$) and hypertension (aOR 2.24 [CI 1.15-4.34], $p=0.017$) (**Table 2**). The only significant factor associated with reporting a past stroke was having diabetes [aOR 3.02 (CI 1.15-7.92), $p=0.025$] while HIV status was not associated with stroke [aOR 1.76 (CI 0.75-4.14), $p=0.193$] (**Table 3**). HIV infection was associated with reporting thrombosis [aOR 2.87 (CI 1.24-6.64), $p=0.014$] (**Table 4**), but not with reporting diabetes [aOR 1.69 (CI 0.87-3.31), $p=0.123$]. Hypertension was the only disease independently associated with diabetes [aOR 2.46 (CI 1.16-5.25), $p=0.020$] (**Table 5**).

There was no significant difference between HIV-negative participants and HIV-positive participants in age at diagnosis of heart disease (median 53 years [IQR 49-64] vs 55 years [IQR 50-59], respectively). In HIV-positive participants, heart disease

occurred at a median of 16 years (IQR 9-19) following HIV diagnosis. Three participants reported heart disease prior to HIV diagnosis. We conducted sensitivity analyses to account for these instances, and found results were not significantly different to the analysis including all participants.

The crude 5-year CVD risk was significantly lower in the HIV-positive cohort [4.0% (IQR 2.8-5.2) vs. 4.4% (IQR 3.1-6.6), $p=0.040$]. After adjusting for age and smoking, HIV status did not significantly influence the mean of the 5-year CVD risk [$\beta=-0.003$ (CI -0.007-0.002), $p=0.298$]. Applying CVD risk evaluation specifically for HIV-positive persons, the 5-year CVD risk for the HIV-positive group increased to 5.4% (IQR 4.0-8.2).

Regarding median levels of biomarkers of systemic inflammation, coagulation and impaired renal function in HIV-positive vs HIV-negative participants, we observed significantly higher levels of hsCRP, (1.6 $\mu\text{g/mL}$ vs 1.1 $\mu\text{g/mL}$, respectively, $p<.001$) and cystatin C (0.94 mg/dL vs 0.86 mg/dL, respectively, $p<.001$). However, no differences were found in median levels of D-dimer and IL-6 (**Table 1**). Figure 1 shows levels of biomarkers by reported heart disease and HIV status. The significant differences in hsCRP and cystatin C remained after excluding people who ever reported heart disease.

Discussion

In our study of older HIV-positive and HIV-negative GBM, HIV infection was independently associated with heart disease and thrombosis. We did not find an association between HIV infection and stroke or DM. Age at diagnosis of heart disease did not vary between the study groups.

Our results are consistent with findings from earlier studies looking at associations between HIV infection and CVD (4, 25-31). However, in contrast to most previous studies, which matched data of HIV-positive patients to the HIV-negative population, we tried to answer remaining questions about the confounding of behavioural factors within the HIV-positive population by applying a prospective data collection approach within a well-defined population.

There was no suggestion of accelerated ageing (conditions occurring at an earlier age) or accelerated atherosclerosis among the HIV-positive group in terms of heart disease. Previous studies of myocardial infarction in people living with and without HIV have also not found an age difference at the time of infarction, just as we found no difference in age at time of diagnosis of heart disease (27, 31). CVD being more prevalent at all ages is indicative of HIV as additional risk factor, accentuating rather than accelerating onset of disease.

While some existing studies found higher rates of DM in people with HIV compared to HIV-negative controls and an independent association of DM and HIV infection (1, 30, 32), we were unable to show similar associations, possibly due to less exposure to NRTIs and PIs associated with DM and to a small number of self-reported DM cases.

Although antiretroviral therapy reduces immune activation in the HIV-positive population, levels of inflammatory markers remain elevated compared to HIV-negative controls (33). D-dimer, hsCRP, IL-6 and cystatin C have all been associated with CVD itself, or with traditional risk factors of CVD in people with HIV (14, 16, 34-36). We found higher levels of hsCRP and cystatin C in HIV-positive participants. Similar findings have been reported by other investigators (7, 37). In contrast there were no differences by HIV status in IL-6 and D-dimer levels in our study. Differences between our study and prior reports may be explained by the fact that this is a group of HIV-positive participants with well-managed disease (97.4% undetectable HIV viral load [<200 copies/mL]) and good immune function, with 70% having CD4 T lymphocyte counts of greater than 500 cells/ μ L). In such cases elevated IL-6 and D-dimer levels were previously reported to be less prevalent (8).

The increased reporting of previously diagnosed heart disease among HIV-positive participants was not reflected in the Framingham CVD risk score. As with previous studies (27, 38), there was no difference between the scores of HIV-positive and HIV-negative participants. This may be indicative of the tendency of the Framingham CVD risk score to underestimate the true risk, and highlights that this calculation should be used with caution in the HIV-positive population. An enhanced approach for risk estimation in this population has been presented by the D:A:D study group (23).

While this study included a well-matched comparable control group of GBM over the age of 55 years, there remain some limitations. First, due to its cross-sectional nature, we could only assess association rather than causality. Second, primary outcome variables were self-reported, and no strict definition of the disease was provided. Likewise, no further details regarding a history of thrombosis were collected. Thrombosis is a common cause of both myocardial infarction (thus likely to have also been reported by participants as past heart disease) and stroke. Thus, participants who had been informed that they had a previous thrombotic stroke or thrombosis of the coronary arteries may have answered yes to multiple questions, when the same thrombotic incident resulted in both outcomes. However, as the questionnaires used by all participants were identical, we believe recall bias should not have been a major issue between groups. Third, HIV-positive and HIV-negative participants may not be comparable due to clinical monitoring advantages of the former and possibly different social determinants and behaviours. Fourth, the HIV-negative participants were not population-based controls but rather recruited at the same clinic sites as the HIV-positive participants and therefore subject to selection bias. Since Australian sexually transmitted infection (STI) and HIV testing guidelines for men who have sex with men (39) recommend at least annual testing, many HIV-negative participants of this study may have attended the participating sites for a routine check-up rather than for a specific illness or other medical issue. Finally, as this study focused on GBM, results may not be generalisable to the entire Australian HIV-positive population.

We found an increased risk for heart disease and thrombosis in the Australian HIV-positive GBM over 55 years of age compared to their HIV-negative peers independent of age. Moving forward, improved screening for, and management of, CVD and DM in HIV-positive GBM should be accompanied by efforts to decrease smoking and improve lipid profiles in this population.

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Table 1. Participant characteristics

	HIV-negative	HIV-positive	P
Patients	189	200	
Age (years)			
Median (IQR)	64.2 (59.7-68.9)	62.1 (58.6-65.9)	0.003
COB			
Australia (%)	130 (68.8)	138 (69.0)	0.327
BMI			
Median (IQR)	26.7 (24.2-29.7)	25.2 (23.5-27.8)	0.002
Waist circumference (cm)			
Median (IQR)	98.5 (90.1-108)	97 (91-104)	0.172
Smoking			
Ever (%)	86 (48.6)	112 (59.6)	0.045
Hypertension			
treated (%)	81 (42.9)	87 (43.5)	0.573
untreated (%)	35 (18.5)	31 (15.5)	
LDL cholesterol (mmol/L)			
Median (IQR)	2.9 (2.3-3.6)	2.6 (1.9-3.3)	0.005
>3.5mmol/L (%)	45 (30.6)	29 (18.0)	0.010
Total cholesterol (mmol/L)			
Median (IQR)	5.0 (4.2-5.7)	4.6 (3.8-5.5)	0.044
>5.5mmol/L (%)	49 (29.9)	45 (26.0)	0.423
HCV antibody positive			
Yes (%)	1 (1.0)	13 (8.2)	0.011
Employment			
Employed (%)	78 (41.3)	80 (40.0)	0.087
Retired (%)	96 (50.8)	90 (45.0)	
Unemployed (%)	15 (7.9)	30 (15.0)	
Exercise (hrs/week)			
Walking median (IQR)	3.4 (1-7)	3 (1.5-6.3)	0.511
Moderate median (IQR)	3 (1-6)	3 (1-6)	0.753
Vigorous median (IQR)	0.5 (0-2)	0 (0-2)	0.923
Pill burden			
Median (IQR)	3 (2-5)	3 (2-5)	0.142
5-year CVD risk (%)			
Framingham median (IQR)	4.4 (3.1-6.6)	4.0 (2.8-5.2)	0.040
D:A:D reduced model median (IQR)	-	5.4 (3.9-8.2)	-
Self-reported comorbidities			
Diabetes (%)	17 (9.0)	30 (15.0)	0.069
Heart disease (%)	23 (12.2)	39 (19.5)	0.048
Stroke (%)	8 (4.2)	15 (7.5)	0.172
Thrombosis (%)	8 (4.2)	21 (10.5)	0.019
Biomarkers			
IL-6 median (IQR)	2.27 (1.77-3.21)	2.33 (1.96-3.14)	0.294
D-dimer median (IQR)	0.37 (0.26-0.53)	0.34 (0.25-0.50)	0.219

hsCRP median (IQR)	1.1 (0.6-2.1)	1.6 (0.7-3.3)	<.001
Cystatin-C median (IQR)	0.86 (0.78-0.95)	0.94 (0.82-1.06)	<.001

Abbreviations: BMI, body mass index; COB, country of birth; CVD, cardiovascular disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; IQR, interquartile range; LDL, low-density lipoprotein;

Table 2. Factors associated with self-reported heart disease, all events.

Predictor	Heart Disease		Univariate analysis			Multivariate analysis		
	No	Yes	OR (95% CI)	p	p (Overall)	OR (95% CI)	p	p (Overall)
Total Patients	327	62 (15.9%)						
HIV status								
negative	166	23 (12.2%)	1			1		
positive	161	39 (19.5%)	1.75 (1.00-3.06)	0.050		1.99 (1.09-3.65)	0.025	
Age group (years)								
55-59	106	17 (13.8%)	1			1		
60-64	99	17 (14.7%)	1.07 (0.52-2.21)	0.854	0.072°	1.00 (0.47-2.14)	0.997	0.048°
65-69	74	13 (14.9%)	1.10 (0.50-2.39)	0.819		1.22 (0.54-2.76)	0.635	
70-74	34	8 (19.1%)	1.47 (0.58-3.70)	0.417		1.51 (0.57-4.01)	0.406	
75+	14	7 (33.3%)	3.12 (1.10-8.84)	0.032		3.66 (1.18-11.4)	0.025	
Smoking								
never	150	17 (10.2%)	1			1		
ever	156	42 (21.2%)	2.38 (1.30-4.36)	0.005	0.017 [#]	2.34 (1.25-4.40)	0.008	0.027 [#]
unknown	21	3 (12.5%)	1.26 (0.34-4.67)	0.729		1.31 (0.35-4.96)	0.690	
Hypertension								
no	130	14 (9.7%)	1			1		
yes	187	47 (20.1%)	2.33 (1.23-4.41)	0.009	0.027 [#]	2.24 (1.15-4.34)	0.017	0.055 [#]
unknown	10	1 (9.1%)	0.93 (0.11-7.80)	0.946		1.23 (0.14-11.0)	0.853	
Pill burden (clinic-reported)								
0	117	8 (6.4%)	1					
1	97	10 (9.4%)	1.51 (0.57-3.97)	0.406	<.001°			
2	61	12 (16.4%)	2.88 (1.12-7.41)	0.029				
3+	52	32 (38.1%)	9.00 (3.88-20.9)	<.001				
Family history								
no	122	16 (11.6%)	1			1		
yes	148	36 (19.6%)	1.86 (0.98-3.50)	0.057	0.155 [#]	1.96 (1.01-3.81)	0.048	0.122 [#]
not (fully) known	57	10 (14.9%)	1.34 (0.57-3.13)	0.503		1.25 (0.52-3.01)	0.618	

° test for trend; [#] test for heterogeneity

Other variables analysed: HIV status/duration, country of birth, alcohol consumption, drug use, HBV infection, HCV infection, diabetes

Abbreviations: CI, confidence interval; OR, odds ratio; HBV hepatitis B virus; HCV, hepatitis C virus;

Table 3. Factors associated with self-reported stroke, all events.

Predictor	Stroke		Univariate analysis			Multivariate analysis (backward sel.)		
	No	Yes	OR (95% CI)	p	p (Overall)	OR (95% CI)	p	p (Overall)
Total Patients	366	23 (5.9%)						
HIV status								
negative	181	8 (4.2%)	1			1		
positive	185	15 (7.5%)	1.83 (0.76-4.43)	0.178		1.76 (0.75-4.14)*	0.193*	
Age group (years)								
55-59	117	6 (4.9%)	1			1		
60-64	111	5 (4.3%)	0.88 (0.26-2.96)	0.834	0.176°	0.87 (0.28-2.71)*	0.805*	0.092*°
65-69	81	6 (6.9%)	1.44 (0.45-4.64)	0.537		1.69 (0.56-5.11)*	0.354*	
70-74	38	4 (9.5%)	2.05 (0.55-7.66)	0.285		2.23 (0.64-7.82)*	0.210*	
75+	19	2 (9.5%)	2.05 (0.39-10.9)	0.399		2.84 (0.58-13.9)*	0.197*	
Smoking								
never	158	9 (5.4%)	1			1		
ever	184	14 (7.1%)	1.31 (0.56-3.06)*	0.531*	0.577*#	1.15 (0.50-2.64)*	0.739*	0.690*#
unknown	24	0 (0.0%)	0.34 (0.02-6.39)*	0.471*		0.36 (0.02-5.69)*	0.467*	
Diabetes								
no	331	17 (4.9%)	1			1		
yes	35	6 (14.6%)	3.34 (1.24-9.02)	0.017		3.02 (1.15-7.92)*	0.025*	
Family history								
no	176	11 (5.9%)	1			1		
yes	130	7 (5.1%)	1.10 (0.50-2.43)	0.812	0.359#	0.92 (0.37-2.32)*	0.864*	0.779*#
not (fully) known	60	5 (7.7%)	0.36 (0.08-1.64)	0.188		1.37 (0.48-3.89)*	0.560*	

* Firth's bias correction; ° test for trend; # test for heterogeneity

Other variables analysed: HIV status/duration, country of birth, alcohol consumption, drug use, HBV infection, HCV infection, hypertension, pill burden

Abbreviations: CI, confidence interval; OR, odds ratio; HBV hepatitis B virus; HCV, hepatitis C virus;

Table 4. Factors associated with self-reported thrombosis, all events.

Predictor	Thrombosis		Univariate analysis			Multivariate analysis (backward sel.)		
	No	Yes	OR (95% CI)	p	p (Overall)	OR (95% CI)	p	p (Overall)
Total Patients	360	29 (7.5%)						
HIV status								
negative	181	8 (4.2%)	1			1		
positive	179	21 (10.5%)	2.65 (1.15-6.15)	0.023		2.87 (1.24-6.64)*	0.014*	
Age group (years)								
55-59	115	8 (6.5%)	1			1		
60-64	109	7 (6.0%)	0.93 (0.34-2.58)	0.890	0.540°	0.86 (0.31-2.41)*	0.770*	0.232*°
65-69	79	8 (9.2%)	1.45 (0.54-3.94)	0.463		1.58 (0.57-4.39)*	0.377*	
70-74	36	6 (14.3%)	2.42 (0.81-7.24)	0.114		2.90 (0.93-9.00)*	0.066*	
75+	21	0 (0.0%)	0.32 (0.02-6.06)	0.445		0.49 (0.03-8.74)*	0.631*	
Smoking								
never	156	11 (6.6%)	1			1		
ever	184	14 (7.1%)	1.08 (0.48-2.45)	0.855	0.229#	1.02 (0.46-2.27)*	0.964*	0.196*#
unknown	20	4 (16.7%)	2.84 (0.83-9.76)	0.098		2.97 (0.85-10.4)*	0.088*	
Hypertension								
no	135	9 (6.3%)	1			1		
yes	217	17 (7.3%)	1.18 (0.51-2.71)	0.705	0.067#	1.20 (0.53-2.71)*	0.669*	0.019*#
unknown	8	3 (27.3%)	5.63 (1.27-24.9)	0.023		9.21 (1.88-45.1)*	0.006*	
Pill burden (clinic-reported)								
0	119	6 (4.8%)	1					
1	103	4 (3.7%)	0.77 (0.21-2.81)	0.692	0.007°			
2	68	5 (6.9%)	1.46 (0.43-4.96)	0.546				
3+	70	14 (16.7%)	3.97 (1.46-10.8)	0.007				
Family history								
no	142	16 (10.1%)	1			1		
yes	33	2 (5.7%)	0.54 (0.12-2.45)	0.423	0.262#	0.68 (0.17-2.74)*	0.588*	0.186*#
not (fully) known	185	11 (5.6%)	0.53 (0.24-1.17)	0.117		0.47 (0.21-1.05)*	0.067*	

* Firth's bias correction; ° test for trend; # test for heterogeneity

Other variables analysed: HIV status/duration, country of birth, alcohol consumption, drug use, HBV infection, HCV infection, diabetes

Abbreviations: CI, confidence interval; OR, odds ratio; HBV hepatitis B virus; HCV, hepatitis C virus;

Table 5. Factors associated with self-reported diabetes, all events.

Predictor	Diabetes		Univariate analysis			Multivariate analysis (backward sel.)		
	No	Yes	OR (95% CI)	p	p (Overall)	OR (95% CI)	p	p (Overall)
Total Patients	342	47 (12.1%)						
HIV status								
negative	172	17 (9.0%)	1			1		
positive	170	30 (15.0%)	1.79 (0.95-3.36)	0.072		1.69 (0.87-3.31)	0.123	
Age group (years)								
55-59	108	15 (12.2%)	1			1		
60-64	100	16 (13.8%)	1.15 (0.54-2.45)	0.713	0.749°	1.04 (0.47-2.31)	0.926	0.955°
65-69	79	8 (9.2%)	0.73 (0.30-1.80)	0.494		0.93 (0.36-2.44)	0.888	
70-74	36	6 (14.3%)	1.20 (0.43-3.33)	0.726		1.11 (0.38-3.24)	0.848	
75+	19	2 (9.5%)	0.76 (0.16-3.59)	0.727		0.85 (0.16-4.36)	0.842	
Smoking								
never	148	19 (11.4%)	1			1		
ever	173	25 (12.6%)	1.13 (0.60-2.13)	0.715	0.934#	1.01 (0.52-1.97)	0.971	0.999#
unknown	21	3 (12.5%)	1.11 (0.30-4.09)	0.872		1.00 (0.26-3.90)	0.998	
Hypertension								
no	134	10 (6.9%)	1			1		
yes	198	36 (15.4%)	2.44 (1.17-5.08)	0.017	0.055#	2.46 (1.16-5.25)	0.020	0.065#
unknown	10	1 (9.1%)	1.34 (0.16-11.6)	0.790		1.78 (0.19-16.4)	0.610	
Pill burden (clinic-reported)								
0	120	5 (4.0%)	1					
1	103	4 (3.7%)	0.93 (0.24-3.56)	0.918	<.001			
2	63	10 (13.7%)	3.81 (1.25-11.6)	0.019				
3+	56	28 (33.3%)	12.0 (4.40-32.7)	<.001				
Family history								
no	164	23 (12.3%)	1			1		
yes	121	16 (11.7%)	4.28 (2.13-8.62)	<.001	<.001#°	4.02 (1.94-8.30)	<.001	0.001#°
not (fully) known	57	8 (12.3%)	1.75 (0.75-4.11)	0.199		1.65 (0.69-3.94)	0.256	

* Firth's bias correction; ° test for trend; # test for heterogeneity

Other variables analysed: HIV status/duration, country of birth, alcohol consumption, drug use, HBV infection, HCV infection, diabetes

Abbreviations: CI, confidence interval; OR, odds ratio; HBV hepatitis B virus; HCV, hepatitis C virus;

Figure 1. Boxplots of biomarkers of systemic inflammation, coagulation and impaired renal function on a log scale.

Abbreviations: HIV, human immunodeficiency virus; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin 6.

The dashed lines indicate the overall means.

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