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The cardiovascular risk management for people living with HIV in Europe: How well are we doing?

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Abstract

Objectives: HIV has become a chronic condition associated with comorbidities. We investigated cardiovascular (CV) risk and risk modification in a European HIV-Cohort. **Methods***:* EuroSIDA patients (from 1/1/2000) for whom CV-risk could be calculated (D:A:D risk equation) were included in the analysis. Moderate to high risk was defined as 5-year CV risk >5% and risk modification as two measurements meeting the European AIDS Clinical Society guidelines. Factors associated with risk development and modifications were investigated using Poisson regression. **Results:** Of 8762 individuals, 32.1% were hypertensive, 45.0% had high cholesterol, 47.4% were current smokers, and 27.1% were

overweight. 1504 (17.2%) had a 5-year CV-risk of > 5%. Of 7258 individuals with a 5-year risk <5%, 1905 (26.2%) developed CV-risk > 5%, (6.53/100 person-years). These patients were more likely to be older, men, living in East Europe, with traditional CV-risk factors. Men who have sex with men, with longer exposure to antiretroviral therapy, low CD4 nadir, higher current CD4, and prior AIDs events were more likely to develop CV-risk. Those on antihypertensive treatment and living in central Europe were less likely to develop CV-risk. Of those clinically indicated for risk modification, 1205/2077(58.0%) successfully modified BP; 1283/3919(32.8%) stopped smoking; 277/1394(19.9%) modified cholesterol and 543/2163(25.1%) reduced their BMI. There was variation in modification of individual risk factors, by gender, age, HIV related factors, and region of follow-up. Risk modification for BP and smoking improved over time (p<0.001). **Conclusion:** CV-risk was common. More than half modified their CV risk and this improved over time.

Keywords: HIV, cardiovascular risk, cohort, antiretoviral therapy, europe

Background

CV disease is the leading cause of death in Europe, accounting for nearly half of all-cause mortality[1]. Prolonged survival due to successful antiretroviral management of people living with HIV (PLHIV) has resulted in a cohort at increased risk of comorbidities and chronic diseases related to aging such as cardiovascular disease[2-6]. Studies suggest that there is a greater prevalence of some modifiable cardiovascular (CV) risk factors in PLHIV and that HIV and/or HIV treatment may be an independent risk factor for CV disease[7-9]. In order to sustain the successes of combination antiretroviral therapy (cART) in reducing mortality and morbidity[2] in PLHIV and accessing care in Europe we need to ensure that there is an equally vigorous approach to the management of the comorbidities associated with HIV and aging, and in particular CV disease.

Patterns of CV risk vary across geographical settings and populations, partly due to genetic factors and partly due to lifestyle and environmental factors[1]. Successful management of CV diseases requires a stepped care approach: primary prevention, identifying risk factors, non-pharmacological management of modifiable risk factors, pharmacological management of risk factors and finally specialist care[10-12]. Although there has been growing awareness of the clustering of health related risk and consequently long-term conditions, integrated management frequently fails. For example, a review found that even in well- functioning health systems less than half of people with diabetes underwent screening and treatment of modifiable CV risk factors[13;14].

PLHIV are followed up regularly, however although this provides the opportunity to manage co-morbidities, we have limited data on stepped care for CV disease: In particular of those identified to have a modifiable risk factor, what proportion achieves modification of their risk factor and what are the predictors of success?

The aim of this paper is to describe the patterns of modifiable CV risk and explore predictors of successful medical management of modifiable risk in HIV positive individuals accessing HIV care within the EuroSIDA cohort.

Methods

Population

The EuroSIDA study is a prospective observational cohort of 18,791 HIV-1 positive adult patients in 108 clinics across 34 European countries, Israel and Argentina. This study has been described previously[15]. In brief, patients were enrolled from nine cohorts from May 1994 onwards. Information is collected onto standardised data collection forms every 6 months, including all CD4 cell counts and viral loads measured since the last follow-up and starting and stopping dates for all cART. For the purposes of this analysis we include all the

individuals enrolled in EuroSIDA after 1/1/2000 for whom at least two measurements of predicted CV risk could be calculated, using two different sets of time-updated variables. The baseline date was considered the date when the risk equation could first be calculated.

Measurement:

Time-updated cardiovascular variables contributing to the construction of the predicted risk estimates were carried forward for a maximum of 12 months. Development of moderate/high CV risk was defined as a predicted 5 year CV risk of over 5% using both D.A.D. and Framingham equations[16;17]. We used a conservative estimate of a predicted 5 year CV risk of 5%- equivalent to a 10 year CV risk of 10%, in order to capture individuals with both moderate and high CV risk. Modifiable risks; hypertension, smoking, high serum cholesterol, diabetes and being overweight, were defined according to European AIDS Clinical society guidelines (Table 1) and successful CV risk modification was defined as two consecutive measurements meeting the same guidelines. Weight loss from a BMI of over 25 to one that is less than 25 was used as a surrogate marker of successful lifestyle interventions (exercise and diet).

Statistical methods:

Baseline associations between risk factors and predicted CV risk were evaluated using logistic regression.

Rates of risk development and risk modification were calculated by dividing the total person years of follow-up (PYFU) with the number of events. Person-time with incomplete covariate data were excluded from the calculation of rates and rate ratios. Individuals were followed until they experienced the outcome of interest for the first time If the outcome of interest did

not occur, individuals were censored 6 months after their last available modifiable risk factor measurement (which equates to their last available risk estimate) or 31/12/2014 whichever occurred first. For the analysis of risk modification, individuals were censored 6 months after their last available measurement of the relevant modifiable risk factor or at 31/12/2014, whichever occurred first. Factors associated with CV risk development and risk modification were investigated using Poisson regression.

All models were adjusted for socio-demographic variables (gender, ethnicity, risk group, region), calendar year, HIV related variables (CD4-cell count, CD4 nadir, prior AIDS diagnosis, prior AIDS or non-AIDS event, cumulative cART exposure, viral load suppression,) hepatitis B and C; and CV-related variables (hypertension and treatment, hyperlipidaemia and treatment, smoking status, BMI, diabetes and Family history of CV disease). All analyses were conducted using SAS 9.3 (Statistical Analysis Software, Cary NC, USA).

Results

Prevalence, incidence and pattern of CV risk

A total of 8762 individuals were included in the analysis. The baseline characteristics can be seen in Table 2. The majority of individuals were male (76.0%), white (87.1%) and had acquired their infection through sex with another man (45.2%).

The prevalence of traditional CV risk factors as defined in table 1 was high; 32.0% of individuals were hypertensive, 27.1% overweight, 45.0% had high cholesterol levels, 5% had diabetes mellitus (DM) and 47.4% were current smokers. At baseline 1504 (17.2%) of

individuals had a moderate to high (5% five year) CV risk according to the D.A.D risk assessment and 1729 (19.7%) according to Framingham's.

After adjustment (figure 1), having a high CV risk at baseline was associated with being male and older age. CD4 Nadir of less that 200 cells/μL, longer duration of cART, current CD4 count of greater than 200 cells/μL and earlier year of entry into the cohort, were also associated with moderate/high CV risk.

Among the 7258 individuals who had a low predicted baseline risk, 1905 (26.2%) went on to develop a moderate/high CV risk, with an overall incidence rate of 6.83 95% CI (6.53-7.34) /100 PYFU. Results from this analysis can be seen in figure 2**.** Individuals who developed moderate to high CV risk were more likely to be, older men, with a family history of CV disease, living in East Europe, with traditional modifiable CV risk factors (smoking, hypertension, high cholesterol, overweight and diabetes). Men who had sex with men, and those with a longer cumulative exposure to cART, with a CD4 nadir of less than 200 cells/μL, current CD4 count of greater than 500 cells/μL and prior AIDS were more likely to develop moderate/high CV risk; whilst there was no relationship between HIV viral load being controlled by cART and the development of CV risk. Those on antihypertensive treatment and living in central Europe were less likely to develop CV risk.

Risk Modification

1205 of 2077 (58.0%) individuals indicated for BP treatment successfully modified their BP, 1283 of 3919 (32.8%) smokers stopped smoking, 277 of 1394 (19.9%) individuals indicated for lipid lowering treatment lowered their cholesterol levels and 543 of 2163 (25.1%) overweight individuals lowered their BMI to below 25.

Blood pressure: In a multivariable Poisson model (table 3a), individuals less likely to modify their blood pressure (BP) were male, older, heterosexual, overweight, with high cholesterol, and diabetes. Those with a family history of CVD and who had a prior CV event were more likely to modify their BP. There was some evidence of regional differences, with individuals from northern Europe less likely to modify their blood pressure as compared to individuals from southern Europe. Those with higher base line BP, those on anti-hypertensive medication and those with CD4 counts of greater than 200 cells/μL were less likely to control BP. There was no association between BP control and HIV viral load. BP control improved over time.

Smoking: Table 3b shows that after adjustment there was good evidence that the rate of smoking cessation differed according to mode of infection and region, with injecting drug users and individuals from eastern Europe less likely to stop smoking. Those with a CD4 nadir of less than 200 cells/μL and detectable viral loads were less likely to stop smoking. Those with a prior CV event were more likely to stop smoking. Rates of smoking cessation improved over time.

Cholesterol: After adjustment (Table 3c): Those with higher CD4 counts and undetectable viral load were less likely to reduce their cholesterol. People with higher baseline cholesterol and diabetes were less likely to successfully reduce their cholesterol. Those with a prior CVD event were more likely to control their cholesterol. There was no evidence for gender or age related differences in modification of cholesterol levels and there was no change in cholesterol modification over time.

Time Trends: We found evidence that modification of blood pressure and smoking increased over time: After adjustment the rate of blood pressure modification increased by 6% per

calendar year (aIRR=1.06, 1.03-1.09, p<0.0001) and the rate of smoking cessation by 5% per year (aIRR=1.05, 1.02-1.07, p<0.0001).

Discussion

This study has demonstrated that the prevalence and incidence of CV risk in people accessing HIV care is very high and only a modest proportion are able to modify any of their CV risk factors. However, risk modification seems to be improving over time. This needs to be interpreted in the context of a relatively robust HIV cascade of care within the same clinical settings, with more than 80% virologically suppressed on cART and despite compelling evidence of the effectiveness of CV risk modification in reducing CV morbidity and mortality. Furthermore, the marked demographic and geographic heterogeneity in CV risk modification has profound implications on equity of care across Europe.

In keeping with other studies the prevalence of CV risk was high[7-9] and heterogeneous across demographics and geography[1]. However, the pattern of modifiable CV risk in this cohort varies considerably from general population estimates. For example, in this cohort the prevalence of smoking and high cholesterol is much higher than the general population, whilst the prevalence of hypertension and obesity is comparable and possibly even lower than the background prevalence[18]. Specifically, in Europe approximately one in three people smoke, compared with one in two in this European cohort of PLHIV. Similarly in the country with the highest prevalence of hypercholesterolemia- Iceland, the general population prevalence is 29%, and the rest of Europe closer to one in five, suggesting that high cholesterol in this cohort was close to double the background prevalence[18]. These differences compared with general population prevalence may partly be explained by the characteristics of the EuroSIDA cohort; however, other HIV cohorts have also found similar high prevalence

of smoking and high cholesterol. Prevalence of hypertension and obesity of one in three is lower than that recorded in the background populations particularly of North and Western Europe[18]. The heterogeneous geographical distribution of modifiable risk factors, however, mirrors that of the background populations[18].

The prevalence and incidence of CV risk was high with 1 in 5 having moderate/high CV risk at baseline and 7% per annum developing moderate to high CV risk. This potentially has huge resource implications for European countries. The WHO Europe region is estimated to have 2.2 million people living with HIV[19] of which extrapolating from this study over 400,000 potentially have moderate/high CV risk, with another 120,000 developing moderate/high CV risk per annum and would require primary CV disease prevention in addition to their ongoing HIV care[19].

On a more positive note, being on antihypertensive treatment was associated with a lower probability of developing CV risk. This mirrors the findings from general population studies. Europe wide data has suggested that whilst there have been guideline driven increases in the prescription of drugs for primary and secondary prevention of CV disease, there remains marked geographic variation in prescription practices, particularly for vulnerable groups such as injection drug users, which is also reflected in the geographic variation in risk modification that we have seen[18]. Whilst earlier diagnosis and more aggressive approaches to CV risk, including smoking cessation and other lifestyle interventions[20], may reduce longer term morbidity and mortality this has resource implications that health systems squeezed by austerity may not be able to invest in, potentially exacerbating existing inequalities in quality of care across people living with HIV and accessing care in Europe.

More than half modified their BP. The health survey of England suggested that only 1/3 modified their BP whilst a review of management of diabetes in Europe found the number

closer to one in four, albeit of the more stringent target of 130/80[21]. However, pilot studies in primary care settings in the UK found that by setting clinical targets, 62% of patients reached the target of 140/90 or less over six months of follow-up, suggesting that whilst HIV clinicians in Europe are doing well, they could do better[22]. The improvement in smoking and BP control over time mirrors the improvement in BP control and smoking cessation in the general population and may also reflect the emphasis and guidance around CV risk management in HIV that has emerged over time. The gender, age and geographical variation in management of BP and other risk, suggests that there are biological, social, cultural and health service related factors that need further investigation. For example to what degree does the poor control in older age reflect the effect of poly-pharmacy and age related metabolic changes on pharmacodynamics and side effects, resulting in poor adherence or variable drug levels in older populations? Alternatively, is this heterogeneity a reflection of the models of care and in particular the varying expertise and experience of managing CV risk in primary care settings compared to specialist HIV and/or infectious disease units? For example, it is notable that those with a history of CVD, i.e. those who are eligible for secondary prevention of CVD were two times more likely to modify their lipids, 50% more likely to stop smoking and 20% more likely to reduce their blood pressure, suggesting room to improve primary prevention.

One aspect that we are unable to directly comment on from this study is the relationship between adherence to cART and successful modification of CV risk factors. On the one hand those who had undetectable HIV viral loads were more likely to stop smoking, perhaps an indication of engagement in care. On the other hand those who successfully managed their HIV, with undetectable viral load and higher CD4 counts, were less able to reduce their cholesterol to recommended levels, perhaps reflecting the effect of some antiretroviral therapy on cholesterol. Unfortunately, we are unable to comment on whether clinicians

switched cART to manage lipids. Overall HIV related factors had less impact on successful reduction in cholesterol than being on a statins.

The limitation of this study should be noted. Although EuroSIDA is one of the larger observational cohorts, CV clinical events were uncommon and therefore we did not have the power to look at the effect of risk modification on CV clinical outcomes. The findings are therefore restricted to CV risk modification and we are unable to comment as to whether CV risk modification is as effective in people living with HIV as has been observed in general population cohorts, further combinations of cohorts would be required to answer this question. Secondly, we have presented the D.A.D risk prediction tool, which is both a conservative estimate of risk (5%, 5 year comparable with a 10%, 10 year Framingham risk) and CV risk tool, which is not in common clinical use. However, in this cohort both medium and high D.A.D CV risk measurements predicted substantial CV events that were higher than those predicted by Framingham's (unpublished data). We repeated our analyses using the Framingham equation and the findings were comparable. Thirdly we were concerned that there would be a risk of channeling bias, with those with higher CV risk being more likely to have a second CV risk measure, however, in fact the opposite was true and they were less likely to have a second CV risk measurement (unpublished data available from the authors). Third, given the numbers of those who had diabetes mellitus (DM) we were unable to look at the risk modification of this important risk factor for cardiovascular disease. However, we note those with DM were 76% less likely to modify their BP, which given the risk of cerebral vascular events and chronic renal failure in this group suggests a need to focus on management of BP in PLHIV and DM. Finally, the patients in the EuroSIDA cohort and in these analyses represent a group of patients who are engaged in care, with good HIV related outcomes, consequently the actual cascade of CV care is likely to be worse than what is reported in this study.

In conclusion, to sustain the morbidity and mortality benefits of antiretroviral therapy we need to tackle the intersecting epidemic of HIV and other comorbidities, including CV risk. Whilst this study suggests that we are improving in recognition and treatment of CV risk, particularly BP and smoking, we need to do much more, particularly for older people, men and those with DM. We need to better understand the reasons for the geographical variation, tackle inequities in access to care, and advocate for the resources needed to manage CV risk. It is important to develop innovative models of patient centered integrated HIV and CV disease care and to evaluate them with both HIV and CV end points in mind.

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Table 1: Definitions of modifiable CV risk factors and risk modification outcomes

Modifiable CV risk factors (for description of study population)	***Clinical indication for risk modification according to EACS guidelines***	***Successful risk modification (Two consecutive measures within 12 months of each other)***
Hypertension (systolic blood pressure (BP) >140 mm Hg, diastolic BP >90 mm Hg or on antihypertensive treatment)	systolic BP >140 or diastolic BP >90 mm Hg	Systolic BP <140 (130 if diabetic) and diastolic BP <90 (<80 if diabetic) mm Hg
High cholesterol (total cholesterol>6 mmol/l, cholesterol:hdl cholesterol ratio >5 or receiving statins)	Predicted 10 year Framingham CV risk of over 20%, diabetic, or established CV disease	Lowering total cholesterol to less than 4 mmol/l
Current smoker	Current smoker	Stopped smoking
Overweight[a] (Body Mass Index (BMI) over 25 kg/m^2)		Lowering BMI to less than 25 kg/m^2 (and more than 18 kg/m^2)

a. Included as an indication of positive lifestyle changes and not based on the EACS guidelines.

Table 2: Characteristics of the Study Population According to Baseline CV Risk

		Total	High Risk (DAD)	High Risk (Framingham)
		N	N (%)	N (%)
Total		**8762**	**1504 (17.2)**	**1729 (19.7)**
Demographics				
Gender	Female	2078	88 (4.2)	116 (5.6)
	Male	6684	1416 (21.2)	1613 (24.1)
Age	Median, IQR	42 (35.7 - 49.9)	56 (50.5 - 62.7)	55 (49.6 - 61.5)
Year of Entry (MM/YY)	Median, IQR	01/06 (05/02-12/08)	01/06 (05/02-08/09)	11/05 (01/02-12/08)
Ethnicity	White	7639	1359 (17.8)	1568 (20.5)
	Non-white	1123	145 (12.9)	161 (14.3)
Mode of Infection	MSM[1]	3957	839 (21.2)	968 (24.5)
	PWID[2]	1486	141 (9.5)	158 (10.6)
	Heterosexual	2705	383 (14.2)	443 (16.4)
	Other/Unknow	614	141 (23.0)	160 (26.1)
European Region[3]	South	2179	310 (14.2)	376 (17.3)
	Central	2543	543 (21.4)	607 (23.9)
	North	1909	460 (24.1)	526 (27.6)
	East	1822	173 (9.5)	185 (10.2)
HIV-related variables				
CD4 group[4]	<200	889	117 (13.2)	152 (17.1)
	200-350	1892	362 (19.1)	383 (20.2)
	350-500	2225	370 (16.6)	441 (19.8)
	>500	3745	654 (17.5)	752 (20.1)
CD4 nadir[5]	<200	5039	1016 (20.2)	1130 (22.4)
	>200	3712	487 (13.1)	598 (16.1)
HIV RNA (cp/ml)[6]	<400	6421	1237 (19.3)	1371 (21.4)
	>400	2276	263 (11.6)	352 (15.5)
Prior AIDS event		2477	551 (22.2)	596 (24.1)
Prior non-AIDS event (not CV)		457	122 (26.7)	118 (25.8)
Cumulative cART exposure	< 1 year	1850	130 (7.0)	968 (24.5)
	1-3 years	1866	198 (10.6)	158 (10.6)
	3-6 years	2643	494 (18.7)	443 (16.4)
	>6 years	2403	682 (28.4)	160 (26.1)
Hepatitis B		501	84 (16.8)	95 (19.0)
Hepatitis C		1488	140 (9.4)	155 (10.4)
Cardio Vascular Disease (CVD) -related variables				
Hypertensive		2811	869 (30.9)	1131 (40.2)
On antihypertensives		864	378 (43.8)	432 (50.0)
High Cholesterol		3950	1058 (26.8)	1252 (31.7)
On lipid lowering drugs		477	197 (41.3)	218 (45.7)
Current Smoker		4152	925 (22.3)	991 (23.9)
Overweight		2371	493 (20.8)	620 (26.1)
Diabetic		487	306 (62.8)	335 (68.8)
Family History of CVD		793	237 (29.9)	171 (21.6)
Prior CVD event		261	141 (54.0)	140 (53.6)

1. MSM=Men Who Have Sex With Men.
2. PWID=Person Who Injects Drugs.
3. Data on 309 individuals from Argentina are not presented here to preserve the anonymity of EuroSIDA countries.
4. 11 individuals had missing CD4 data at baseline.
5. 11 individuals had missing CD4 nadir data at baseline.
6. 65 individuals had missing RNA values at baseline

Table 3a. Incidence Rates and Rate Ratios for modifying blood pressure

		N	PYFU	Rate (95%CI) per 100 PYFU	Univariable		Multivariable	
					RR (95%CI)	P-value	RR (95%CI)	P-value
Total		***1204***	***7668***	***15.70 (14.84 - 16.61)***				
Gender	Female	222.0	1055	21.04 (18.45 - 24.00)	1.00		1.00	
	Male	982.0	6613	14.85 (13.95 - 15.81)	0.71 (0.61 - 0.82)	<.001	0.68 (0.57 - 0.81)	<.001
Age at baseline	Per 10 years				0.75 (0.71 - 0.80)	<.001	0.90 (0.85 - 0.96)	0.002
Year	2000-2001	47.0	431.2	10.90 (8.19 - 14.51)	1.00		1.00	
	2002-2003	164.0	875.9	18.72 (16.07 - 21.82)	1.72 (1.24 - 2.38)	0.001	1.87 (1.35 - 2.59)	<.001
	2004-2005	181.0	1017	17.80 (15.39 - 20.59)	1.63 (1.18 - 2.25)	0.003	2.02 (1.45 - 2.82)	<.001
	2006-2007	190.0	1153	16.49 (14.30 - 19.00)	1.51 (1.10 - 2.08)	0.011	2.09 (1.49 - 2.91)	<.001
	2008-2009	184.0	1293	14.23 (12.32 - 16.45)	1.31 (0.95 - 1.80)	0.103	1.91 (1.36 - 2.68)	<.001
	2010-2011	189.0	1214	15.57 (13.50 - 17.95)	1.43 (1.04 - 1.97)	0.029	2.22 (1.57 - 3.13)	<.001
	2012-2014	249.0	1684	14.78 (13.06 - 16.74)	1.36 (0.99 - 1.85)	0.055	2.02 (1.44 - 2.83)	<.001
Ethnicity	White	1083	6808	15.91 (14.99 - 16.88)	1.00		1.00	
	Non-white	121.0	860.1	14.07 (11.77 - 16.81)	0.88 (0.73 - 1.07)	0.200	0.94 (0.76 - 1.16)	0.563
Mode of Infection	MSM	572.0	3813	15.00 (13.82 - 16.28)	1.00		1.00	
	PWID	194.0	775.3	25.02 (21.74 - 28.80)	1.67 (1.42 - 1.96)	<.001	1.05 (0.83 - 1.33)	0.694
	Heterosexual	339.0	2427	13.97 (12.55 - 15.53)	0.93 (0.81 - 1.06)	0.297	0.81 (0.69 - 0.95)	0.010
	Other/Unknown	99.0	651.7	15.19 (12.48 - 18.50)	1.01 (0.82 - 1.25)	0.907	0.94 (0.76 - 1.18)	0.615
Region	South	292.0	1653	17.66 (15.75 - 19.81)	1.00		1.00	
	Central	380.0	2354	16.14 (14.60 - 17.85)	0.91 (0.78 - 1.06)	0.248	0.94 (0.80 - 1.11)	0.463
	North	261.0	2326	11.22 (9.94 - 12.67)	0.64 (0.54 - 0.75)	<.001	0.66 (0.55 - 0.79)	<.001
	East	241.0	1178	20.45 (18.03 - 23.20)	1.16 (0.98 - 1.37)	0.092	0.95 (0.79 - 1.14)	0.553
HIV-related variables								
CD4 group	<200	83.0	420.0	19.76 (15.94 - 24.51)	1.00		1.00	
	200-350	200.0	1261	15.85 (13.80 - 18.21)	0.80 (0.62 - 1.04)	0.092	0.75 (0.58 - 0.98)	0.035
	350-500	285.0	1877	15.19 (13.52 - 17.06)	0.77 (0.60 - 0.98)	0.035	0.72 (0.56 - 0.93)	0.012
	>500	636.0	4108	15.48 (14.32 - 16.73)	0.78 (0.62 - 0.98)	0.036	0.74 (0.57 - 0.94)	0.016
CD4 nadir	<200	686.0	4599	14.92 (13.84 - 16.08)	1.00		1.00	
	>200	516.0	3061	16.86 (15.47 - 18.38)	1.13 (1.01 - 1.27)	0.036	1.11 (0.97 - 1.27)	0.137
HIV RNA (cp/ml)	<400 (suppressed)	1010	6636	15.22 (14.31 - 16.19)	1.00		1.00	
	>400	193.0	1024	18.85 (16.37 - 21.71)	1.24 (1.06 - 1.44)	0.006	1.06 (0.89 - 1.26)	0.536
Prior AIDS event	No	869.0	5410	16.06 (15.03 - 17.17)	1.00		1.00	
	Yes	335.0	2258	14.84 (13.33 - 16.51)	0.92 (0.81 - 1.05)	0.217	0.96 (0.84 - 1.10)	0.573
Prior non-AIDS event (not	No	1140	7317	15.58 (14.70 - 16.51)	1.00		1.00	
	Yes	64.0	350.8	18.24 (14.28 - 23.31)	1.17 (0.91 - 1.51)	0.220	1.18 (0.91 - 1.53)	0.220
Cumulative cART exposure	<1 year	96.0	524.5	18.30 (14.98 - 22.36)	1.00		1.00	

	1-3 years	150.0	783.1	19.16 (16.32 - 22.48)	1.05 (0.81 - 1.35)	0.728	1.15 (0.88 - 1.51)	0.316
	3-6 years	325.0	1832	17.74 (15.92 - 19.78)	0.97 (0.77 - 1.22)	0.789	1.24 (0.97 - 1.60)	0.087
	>6 years	633.0	4528	13.98 (12.93 - 15.11)	0.76 (0.62 - 0.95)	0.014	1.10 (0.86 - 1.41)	0.444
Hepatitis B	No	1063	6868	15.48 (14.58 - 16.44)	1.00		1.00	
	Yes	82.0	416.9	19.67 (15.84 - 24.42)	1.27 (1.02 - 1.59)	0.037	1.15 (0.91 - 1.45)	0.233
	Unknown	59.0	383.0	15.40 (11.94 - 19.88)	1.00 (0.77 - 1.29)	0.972	0.86 (0.65 - 1.13)	0.280
Hepatitis C	No	799.0	5492	14.55 (13.57 - 15.59)	1.00		1.00	
	Yes	207.0	902.2	22.94 (20.02 - 26.29)	1.58 (1.35 - 1.84)	<.001	1.10 (0.88 - 1.37)	0.415
	Unknown	198.0	1274	15.55 (13.52 - 17.87)	1.07 (0.91 - 1.25)	0.404	0.97 (0.82 - 1.15)	0.740
CVD-related variables (all baseline)								
Blood Pressure								
	Per 10				0.77 (0.74 - 0.81)	<.001	0.82 (0.78 - 0.86)	<.001
On antihypertensives	No	1035	6115	16.92 (15.92 - 17.99)	1.00		1.00	
	Yes	169.0	1552	10.89 (9.36 - 12.66)	0.64 (0.55 - 0.76)	<.001	0.84 (0.70 - 0.99)	0.043
High Cholesterol	No	583.0	3142	18.56 (17.11 - 20.13)	1.00		1.00	
	Yes	621.0	4526	13.72 (12.68 - 14.84)	0.74 (0.66 - 0.83)	<.001	0.86 (0.76 - 0.98)	0.018
On lipid lowering drugs	No	1133	7084	15.99 (15.09 - 16.95)	1.00		1.00	
	Yes	71.0	583.2	12.17 (9.65 - 15.36)	0.76 (0.60 - 0.97)	0.026	0.98 (0.76 - 1.26)	0.884
Current Smoker	No	625.0	4419	14.14 (13.08 - 15.30)	1.00		1.00	
	Yes	559.0	3098	18.04 (16.61 - 19.60)	1.28 (1.14 - 1.43)	<.001	1.03 (0.91 - 1.17)	0.592
	Ex	20.0	150.8	13.26 (8.55 - 20.55)	0.94 (0.60 - 1.46)	0.776	0.82 (0.52 - 1.30)	0.405
Overweight	No	806.0	4328	18.62 (17.38 - 19.95)	1.00		1.00	
	Yes	398.0	3340	11.92 (10.80 - 13.15)	0.64 (0.57 - 0.72)	<.001	0.76 (0.67 - 0.86)	<.001
Diabetic	No	1149	6302	18.23 (17.21 - 19.32)	1.00		1.00	
	Yes	55.0	1366	4.03 (3.09 - 5.24)	0.22 (0.17 - 0.29)	<.001	0.24 (0.18 - 0.31)	<.001
Family History of CVD	No	1060	6966	15.22 (14.33 - 16.16)	1.00		1.00	
	Yes	144.0	701.3	20.53 (17.44 - 24.18)	1.35 (1.13 - 1.61)	<.001	1.23 (1.03 - 1.47)	0.021
Prior CVD event	No	1119	7064	15.84 (14.94 - 16.80)	1.00		1.00	
	Yes	85.0	603.5	14.08 (11.39 - 17.42)	0.89 (0.71 - 1.11)	0.296	1.60 (1.27 - 2.02)	<.001

Table 3b. Incidence Rates and Rate Ratios for stopping smoking

		N	PYFU	Rate (95%CI) per 100 PYFU	Univariable		Multivariable	
					RR (95%CI)	P-value	RR (95%CI)	P-value
Total		***1283***	***20850***	***6.15 (5.83 - 6.50)***				
Gender	Female	264.0	4440	5.95 (5.27 - 6.71)				
	Male	1019	16410	6.21 (5.84 - 6.60)	1.04 (0.91 - 1.20)	0.530	0.93 (0.80 - 1.10)	0.407
Age at baseline	Per 10 years				1.12 (1.06 - 1.19)	<.001	1.02 (0.95 - 1.09)	0.631
Year	2000-2001	84.0	897.6	9.36 (7.56 - 11.59)	2.46 (1.82 - 3.34)	<.001	2.46 (1.81 - 3.35)	<.001
	2002-2003	81.0	2133	3.80 (3.05 - 4.72)				
	2004-2005	129.0	2966	4.35 (3.66 - 5.17)	1.15 (0.87 - 1.51)	0.338	1.10 (0.83 - 1.45)	0.526
	2006-2007	195.0	3217	6.06 (5.27 - 6.97)	1.60 (1.23 - 2.07)	<.001	1.50 (1.15 - 1.96)	0.003
	2008-2009	248.0	3353	7.40 (6.53 - 8.38)	1.95 (1.52 - 2.50)	<.001	1.79 (1.38 - 2.33)	<.001
	2010-2011	221.0	3341	6.62 (5.80 - 7.55)	1.74 (1.35 - 2.25)	<.001	1.60 (1.23 - 2.09)	<.001
	2012-2014	325.0	4943	6.58 (5.90 - 7.33)	1.73 (1.36 - 2.21)	<.001	1.60 (1.23 - 2.07)	<.001
Ethnicity	White	1182	19253	6.14 (5.80 - 6.50)				
	Non-white	101.0	1597	6.33 (5.20 - 7.69)	1.03 (0.84 - 1.26)	0.774	0.97 (0.78 - 1.21)	0.814
Mode of Infection	MSM	583.0	8709	6.69 (6.17 - 7.26)				
	PWID	286.0	6045	4.73 (4.21 - 5.31)	0.71 (0.61 - 0.81)	<.001	0.74 (0.60 - 0.91)	0.005
	Heterosexual	348.0	5055	6.88 (6.20 - 7.65)	1.03 (0.90 - 1.17)	0.680	1.00 (0.85 - 1.17)	0.999
	Other/Unknown	66.0	1041	6.34 (4.98 - 8.07)	0.95 (0.73 - 1.22)	0.678	0.99 (0.76 - 1.28)	0.921
European Region	South	370.0	5953	6.22 (5.61 - 6.88)				
	Central	327.0	5162	6.33 (5.68 - 7.06)	1.02 (0.88 - 1.18)	0.802	0.98 (0.84 - 1.15)	0.827
	North	310.0	4218	7.35 (6.58 - 8.21)	1.18 (1.02 - 1.38)	0.030	1.12 (0.95 - 1.31)	0.167
	East	226.0	5056	4.47 (3.92 - 5.09)	0.72 (0.61 - 0.85)	<.001	0.75 (0.63 - 0.89)	<.001
HIV-related variables								
CD4 group	<200	90.0	1466	6.14 (4.99 - 7.55)				
	200-350	193.0	3255	5.93 (5.15 - 6.83)	0.97 (0.75 - 1.24)	0.787	0.89 (0.69 - 1.15)	0.363
	350-500	287.0	4501	6.38 (5.68 - 7.16)	1.04 (0.82 - 1.32)	0.752	0.90 (0.70 - 1.15)	0.384
	>500	713.0	11627	6.13 (5.70 - 6.60)	1.00 (0.80 - 1.24)	0.994	0.76 (0.60 - 0.97)	0.025
CD4 nadir	<200	711.0	12220	5.82 (5.41 - 6.26)				
	>200	571.0	8615	6.63 (6.11 - 7.19)	1.14 (1.02 - 1.27)	0.020	1.27 (1.12 - 1.45)	<.001
HIV RNA (cp/ml)	<400 (suppressed)	1102	17248	6.39 (6.02 - 6.78)				
	>400	178.0	3539	5.03 (4.34 - 5.83)	0.79 (0.67 - 0.92)	0.003	0.81 (0.68 - 0.97)	0.022
Prior AIDS event	No	910.0	15073	6.04 (5.66 - 6.44)				
	Yes	373.0	5778	6.46 (5.83 - 7.15)	1.07 (0.95 - 1.21)	0.276	1.10 (0.97 - 1.26)	0.135
Prior non-AIDS event (not CV)	No	1226	19804	6.19 (5.85 - 6.55)				
	Yes	57.0	1046	5.45 (4.20 - 7.07)	0.88 (0.68 - 1.15)	0.347	0.85 (0.65 - 1.11)	0.228

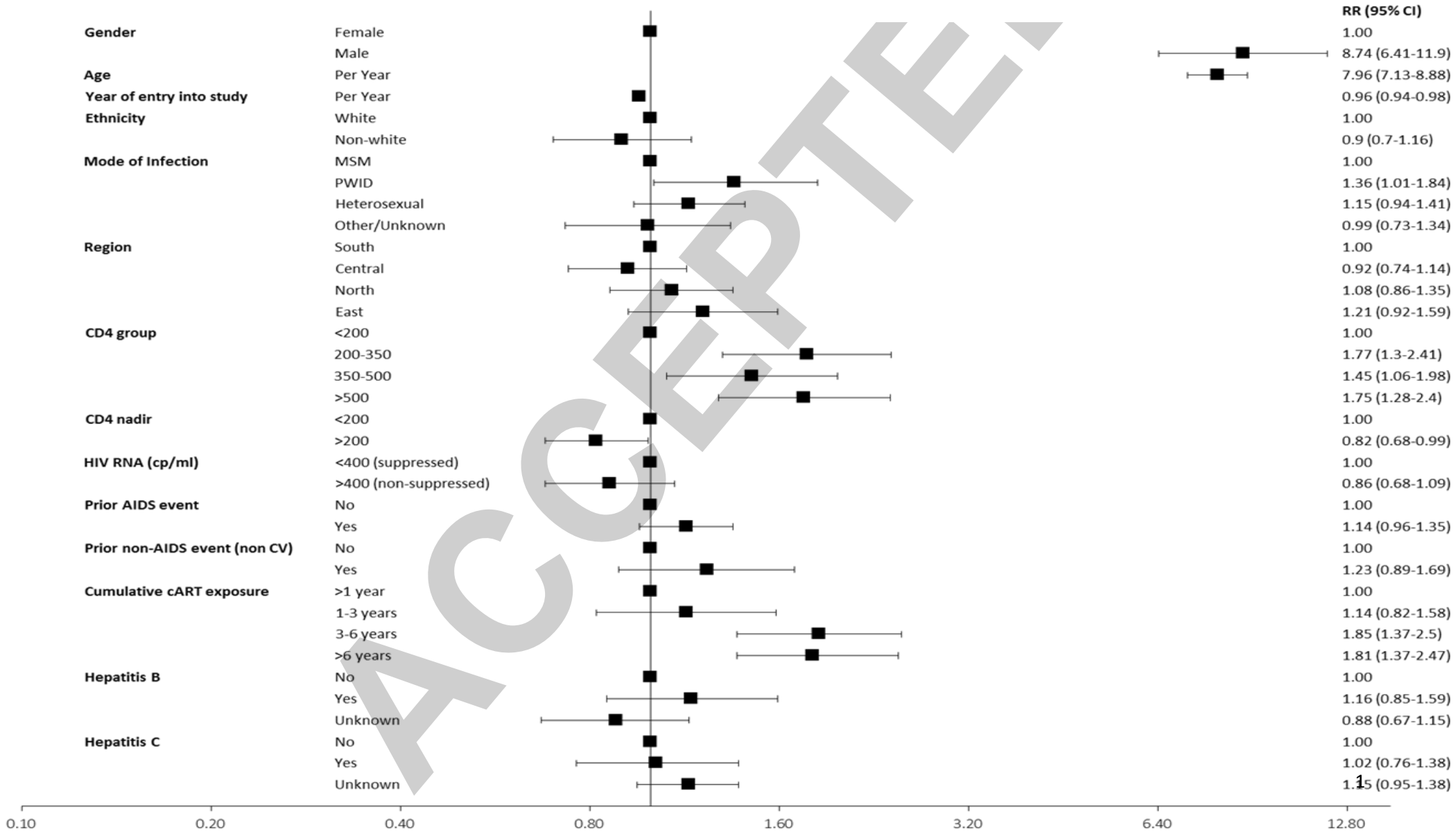
Cumulative cART exposure	<1 year	83.0	1617	5.13 (4.14 - 6.37)				
	1-3 years	132.0	2221	5.94 (5.01 - 7.05)	1.16 (0.88 - 1.52)	0.295	1.13 (0.85 - 1.51)	0.412
	3-6 years	283.0	5101	5.55 (4.94 - 6.23)	1.08 (0.85 - 1.38)	0.533	1.11 (0.85 - 1.45)	0.433
	>6 years	785.0	11912	6.59 (6.15 - 7.07)	1.28 (1.02 - 1.61)	0.030	1.24 (0.96 - 1.61)	0.099
Hepatitis B	No	1126	18123	6.21 (5.86 - 6.59)				
	Yes	91.0	1592	5.72 (4.66 - 7.02)	0.92 (0.74 - 1.14)	0.445	0.93 (0.75 - 1.15)	0.498
	Unknown	66.0	1135	5.81 (4.57 - 7.40)	0.94 (0.73 - 1.20)	0.599	1.01 (0.79 - 1.31)	0.916
Hepatitis C	No	777.0	11466	6.78 (6.32 - 7.27)				
	Yes	317.0	6256	5.07 (4.54 - 5.66)	0.75 (0.66 - 0.85)	<.001	1.01 (0.83 - 1.22)	0.957
	Unknown	189.0	3128	6.04 (5.24 - 6.97)	0.89 (0.76 - 1.05)	0.158	0.99 (0.84 - 1.17)	0.898
CVD-related variables (all baseline)								
Hypertension	No	904.0	15300	5.91 (5.54 - 6.31)				
	Yes	379.0	5550	6.83 (6.17 - 7.55)	1.16 (1.03 - 1.30)	0.018	1.12 (0.98 - 1.28)	0.102
On antihypertensives	No	1200	19561	6.13 (5.80 - 6.49)				
	Yes	83.0	1289	6.44 (5.19 - 7.99)	1.05 (0.84 - 1.31)	0.668	0.80 (0.62 - 1.03)	0.088
High Cholesterol	No	666.0	11174	5.96 (5.52 - 6.43)				
	Yes	617.0	9677	6.38 (5.89 - 6.90)	1.07 (0.96 - 1.19)	0.228	0.97 (0.86 - 1.10)	0.650
On lipid lowering drugs	No	1219	19968	6.10 (5.77 - 6.46)				
	Yes	64.0	882.3	7.25 (5.68 - 9.27)	1.19 (0.92 - 1.53)	0.179	1.09 (0.84 - 1.43)	0.506
Overweight	No	962.0	16176	5.95 (5.58 - 6.33)				
	Yes	321.0	4674	6.87 (6.16 - 7.66)	1.15 (1.02 - 1.31)	0.025	1.10 (0.97 - 1.26)	0.147
Diabetic	No	1188	19693	6.03 (5.70 - 6.39)				
	Yes	95.0	1157	8.21 (6.72 - 10.04)	1.36 (1.10 - 1.68)	0.004	1.21 (0.98 - 1.51)	0.083
Family History of CVD	No	1149	18600	6.18 (5.83 - 6.55)				
	Yes	134.0	2250	5.96 (5.03 - 7.05)	0.96 (0.81 - 1.15)	0.689	0.97 (0.81 - 1.16)	0.743
Prior CVD event	No	1196	19986	5.98 (5.65 - 6.33)				
	Yes	87.0	863.8	10.07 (8.16 - 12.43)	1.68 (1.35 - 2.09)	<.001	1.50 (1.19 - 1.89)	<.001

Table 3c. Incidence Rates and Rate Ratios for reducing cholesterol

		N	PYFU	Rate (95%CI) per 100 PYFU	Univariable		Multivariable	
					RR (95%CI)	P-value	RR (95%CI)	P-value
Total		***277.0***	***7907***	***3.50 (3.11 - 3.94)***				
Gender	Female	26.0	690.7	3.76 (2.56 - 5.53)				
	Male	251.0	7216	3.48 (3.07 - 3.94)	0.92 (0.62 - 1.38)	0.701	1.33 (0.84 - 2.09)	0.221
Age at baseline	Per 10 years				0.85 (0.76 - 0.97)	0.013	1.02 (0.89 - 1.16)	0.792
Year	2000-2001	14.0	344.7	4.06 (2.41 - 6.86)				
	2002-2003	36.0	773.0	4.66 (3.36 - 6.46)	1.15 (0.62 - 2.13)	0.664	1.28 (0.68 - 2.39)	0.444
	2004-2005	20.0	1032	1.94 (1.25 - 3.00)	0.48 (0.24 - 0.94)	0.034	0.56 (0.27 - 1.15)	0.114
	2006-2007	52.0	1244	4.18 (3.19 - 5.49)	1.03 (0.57 - 1.86)	0.924	1.21 (0.63 - 2.33)	0.565
	2008-2009	48.0	1324	3.63 (2.73 - 4.81)	0.89 (0.49 - 1.62)	0.708	1.14 (0.58 - 2.23)	0.712
	2010-2011	36.0	1281	2.81 (2.03 - 3.90)	0.69 (0.37 - 1.28)	0.242	0.88 (0.44 - 1.77)	0.717
	2012-2014	71.0	1908	3.72 (2.95 - 4.70)	0.92 (0.52 - 1.62)	0.764	1.13 (0.58 - 2.21)	0.716
Ethnicity	White	250.0	7186	3.48 (3.07 - 3.94)				
	Non-white	27.0	720.9	3.75 (2.57 - 5.46)	1.08 (0.72 - 1.60)	0.716	1.00 (0.65 - 1.52)	0.982
Mode of Infection	MSM	138.0	4405	3.13 (2.65 - 3.70)				
	PWID	47.0	520.3	9.03 (6.79 - 12.02)	2.88 (2.07 - 4.01)	<.001	1.67 (1.04 - 2.68)	0.032
	Heterosexual	65.0	2258	2.88 (2.26 - 3.67)	0.92 (0.68 - 1.23)	0.574	0.74 (0.53 - 1.03)	0.074
	Other/Unknown	27.0	724.1	3.73 (2.56 - 5.44)	1.19 (0.79 - 1.80)	0.408	0.95 (0.62 - 1.45)	0.807
European Region	South	80.0	2063	3.88 (3.11 - 4.83)				
	Central	102.0	2704	3.77 (3.11 - 4.58)	0.97 (0.73 - 1.30)	0.854	1.10 (0.80 - 1.53)	0.558
	North	65.0	2140	3.04 (2.38 - 3.87)	0.78 (0.56 - 1.09)	0.143	1.12 (0.78 - 1.61)	0.533
	East	29.0	903.9	3.21 (2.23 - 4.62)	0.83 (0.54 - 1.27)	0.382	1.22 (0.78 - 1.93)	0.383
HIV-related variables								
CD4 group	<200	36.0	435.4	8.27 (5.96 - 11.46)				
	200-350	52.0	1308	3.98 (3.03 - 5.22)	0.48 (0.31 - 0.74)	<.001	0.56 (0.36 - 0.86)	0.009
	350-500	71.0	1863	3.81 (3.02 - 4.81)	0.46 (0.31 - 0.69)	<.001	0.58 (0.38 - 0.90)	0.015
	>500	118.0	4300	2.74 (2.29 - 3.29)	0.33 (0.23 - 0.48)	<.001	0.42 (0.27 - 0.65)	<.001
CD4 nadir	<200	178.0	5137	3.47 (2.99 - 4.01)				
	>200	99.0	2762	3.58 (2.94 - 4.37)	1.03 (0.81 - 1.32)	0.787	1.05 (0.78 - 1.41)	0.747
HIV RNA (cp/ml)	<400 (suppressed)	222.0	7056	3.15 (2.76 - 3.59)				
	>400	55.0	845.3	6.51 (5.00 - 8.48)	2.07 (1.54 - 2.78)	<.001	1.64 (1.16 - 2.33)	0.005
Prior AIDS event	No	174.0	5168	3.37 (2.90 - 3.91)				

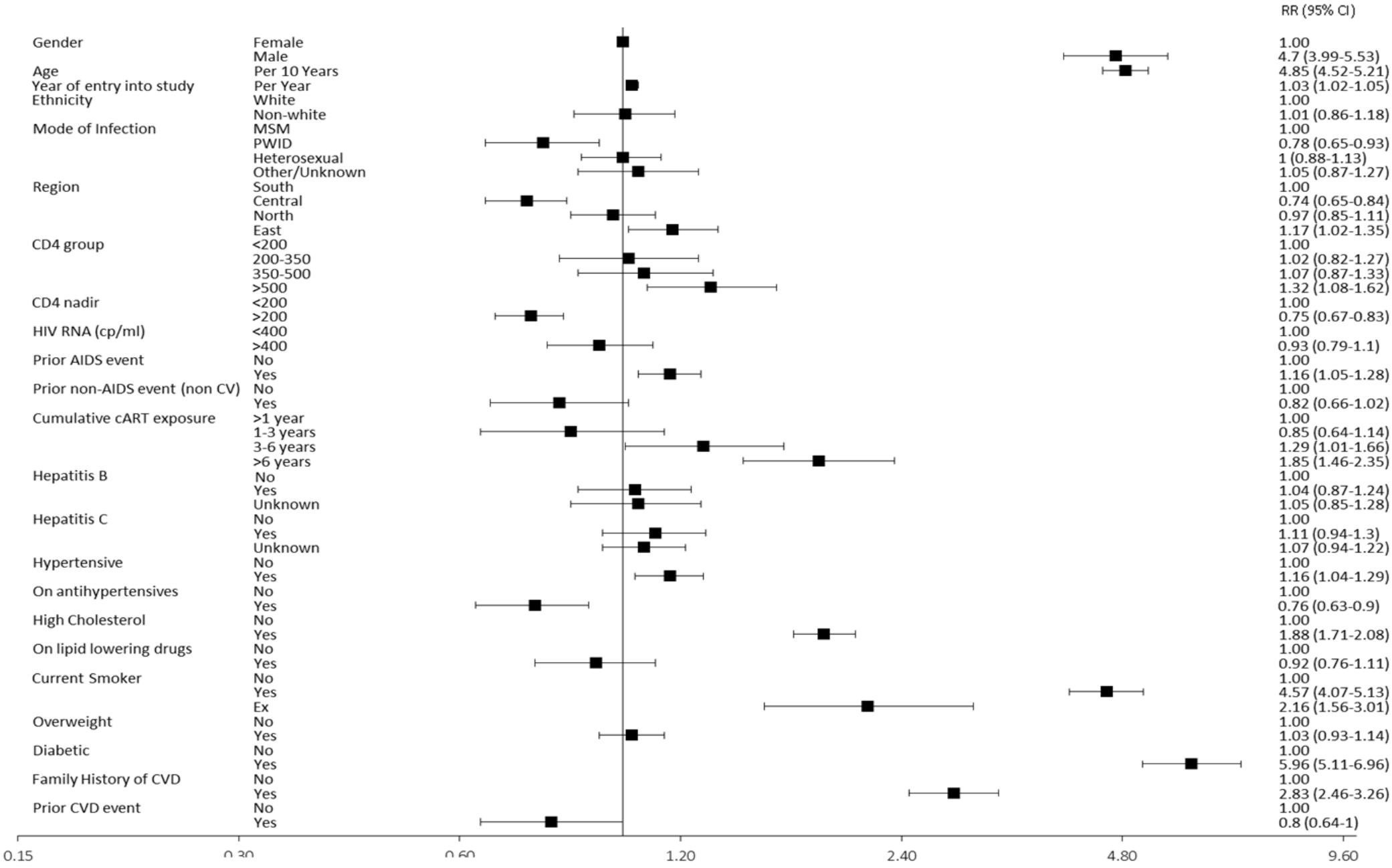
	Yes	103.0	2739	3.76 (3.10 - 4.56)	1.12 (0.88 - 1.43)	0.373	1.11 (0.85 - 1.44)	0.459
Prior non-AIDS event (not CV)	No	250.0	7386	3.38 (2.99 - 3.83)				
	Yes	27.0	520.7	5.18 (3.56 - 7.56)	1.53 (1.03 - 2.28)	0.035	1.50 (0.99 - 2.28)	0.056
Cumulative cART exposure	lt1 year	19.0	274.7	6.92 (4.41 - 10.84)				
	1-3 years	20.0	398.5	5.02 (3.24 - 7.78)	0.73 (0.39 - 1.36)	0.317	0.88 (0.46 - 1.69)	0.707
	3-6 years	51.0	1399	3.64 (2.77 - 4.80)	0.53 (0.31 - 0.89)	0.017	0.62 (0.35 - 1.10)	0.103
	>6 years	187.0	5834	3.21 (2.78 - 3.70)	0.46 (0.29 - 0.74)	0.001	0.60 (0.35 - 1.03)	0.062
Hepatitis B	No	244.0	7079	3.45 (3.04 - 3.91)				
	Yes	22.0	494.2	4.45 (2.93 - 6.76)	1.29 (0.83 - 2.00)	0.250	1.24 (0.79 - 1.95)	0.354
	Unknown	11.0	334.0	3.29 (1.82 - 5.95)	0.96 (0.52 - 1.75)	0.882	0.77 (0.41 - 1.46)	0.425
Hepatitis C	No	175.0	5984	2.92 (2.52 - 3.39)				
	Yes	54.0	595.4	9.07 (6.95 - 11.84)	3.10 (2.29 - 4.21)	<.001	1.48 (0.96 - 2.26)	0.075
	Unknown	48.0	1328	3.62 (2.72 - 4.80)	1.24 (0.90 - 1.70)	0.193	1.00 (0.71 - 1.41)	0.997
CVD-related variables (all baseline)								
Hypertension	No	92.0	2800	3.29 (2.68 - 4.03)				
	Yes	185.0	5107	3.62 (3.14 - 4.18)	1.10 (0.86 - 1.42)	0.445	1.17 (0.87 - 1.58)	0.310
On antihypertensives	No	186.0	5665	3.28 (2.84 - 3.79)				
	Yes	91.0	2242	4.06 (3.30 - 4.98)	1.24 (0.96 - 1.59)	0.098	0.97 (0.71 - 1.32)	0.830
High Cholesterol								
	Per 10				0.58 (0.52 - 0.63)	<.001	0.62 (0.56 - 0.68)	<.001
On lipid lowering drugs	No	238.0	6894	3.45 (3.04 - 3.92)				
	Yes	39.0	1013	3.85 (2.81 - 5.27)	1.12 (0.80 - 1.57)	0.526	0.92 (0.64 - 1.32)	0.640
Current Smoker	No	123.0	3624	3.39 (2.84 - 4.05)				
	Yes	152.0	4094	3.71 (3.17 - 4.35)	1.09 (0.86 - 1.39)	0.459	1.18 (0.91 - 1.54)	0.209
	Ex	2.0	188.8	1.06 (0.27 - 4.24)	0.31 (0.08 - 1.26)	0.102	0.23 (0.06 - 0.97)	0.045
Overweight	No	171.0	4836	3.54 (3.04 - 4.11)				
	Yes	106.0	3071	3.45 (2.85 - 4.18)	0.98 (0.77 - 1.24)	0.846	1.02 (0.79 - 1.31)	0.892
Diabetic	No	142.0	5168	2.75 (2.33 - 3.24)				
	Yes	135.0	2739	4.93 (4.16 - 5.84)	1.79 (1.42 - 2.27)	<.001	1.85 (1.42 - 2.40)	<.001
Family History of CVD	No	238.0	7094	3.35 (2.95 - 3.81)				
	Yes	39.0	812.8	4.80 (3.51 - 6.57)	1.43 (1.02 - 2.01)	0.038	1.22 (0.86 - 1.74)	0.268
Prior CVD event	No	181.0	6350	2.85 (2.46 - 3.30)				
	Yes	96.0	1557	6.17 (5.05 - 7.53)	2.16 (1.69 - 2.77)	<.001	1.98 (1.50 - 2.61)	<.001

Figure 1. Baseline Factor Associated with a High CV risk (DAD) in Multivariable[1] Logistic Regression Models



1. The model was adjusted for all the factors listed in the Figure

Figure 2: Factors associated with the development of a high CV risk (DAD) in Multivariable[1] Poisson Regression Model



1. The model was adjusted for all the factors listed in the Figure

Appendix: Tables and Figures

Appendix Table 1: Formulas used to calculate the predicted risk estimates

Risk Equation	**Formulas and code**[1]
Framingham (5-year)	**Equation and variables needed** (Reproduced from Anderson et al, 1991) **Framingham (1991) risk equation:** $1 - exp(-exp(u))$ $u = \frac{log(t) - \mu}{\sigma}$ $where\ \ \mu = \beta_0 + \beta_1 x_1 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_5 + \beta_6 x_6 + \beta_7 x_7 + \beta_8 x_8 + \beta_9 x_9 + \beta_{10} x_{10} + \beta_{11} x_{11} + \beta_{12} x_{12}$ $log(\sigma) = \theta + (\theta_1 \cdot \mu)$ **β and θ constant values and variables needed:**

Constants	CVD	Coefficients (x)
θ_0	0.6536	
θ_1	-0.2404	
β_0	18.8144	
β_1	-1.2146	Female
β_2	-1.8443	Log(age)
β_3	---	Log(age)^2
β_4	0.3668	Log(age) x female
β_5	---	(Log(age))^2 x female
β_6	-1.4032	Log(systolic blood pressure)
β_7	-0.3899	Cigarettes (Y/N)
β_8	-0.5390	Log(total cholesterol/HDL cholesterol
β_9	-0.3036	Diabetes
β_{10}	-0.1697	Diabetes x female
β_{11}	-0.3362	ECG-LVH
β_{12}	---	ECG-LVH x male

	Notes on equation set up:
	SBP is entered in mmHg, Total and HDL cholesterol in mg/dl
	SAS code
	(A Schultze, Oct. 2015)
	
	`/*Variables used:`
	`framgend=gender (1=female, 0=male)`
	`rcurrage=age in years`
	`rbp=systolic blood pressure`
	`rhdl=hdl cholesterol`
	`rch=total cholesterol`
	`rdia=diabetes (1=yes, 0=No);`
	`lvh=ECG left ventricular hypertrophy`
	`*/`
	
	`*total chol and hdl chol in mg/dl;`
	`if rch ne . then frch=rch*38.66976;`
	`if rhdl ne . then frhdl=rhdl*38.66976;`
	
	`if frch ge 0 & frhdl ge 0 then do;`
	`ratio=(frch/frhdl);`
	
	`*the prevalence of LVH, a rare condition, is presumed to be zero (Matthew Law, personal communication);`
	`lvh=0;`
	
	`theta0=0.6536;`
	`theta1=-0.2402;`
	`bet0=18.8144;`
	`female=-1.2146*framgend;`
	`lnage=(-1.8443*(log(rcurrage)));`
	`lnagefem=(0.3668*(log(rcurrage))*framgend;`
	`lnsbp=-1.4032*log(rbp);`
	`cig=-0.3899*risksmok;`
	`lntchdl=-0.5390*(log(ratio));`
	`dbetes=-0.3036*rdia;`
	`dbetesfem=-0.1697*(rdia*framgend);`
	`ecg_lvh=-0.3362*lvh;`
	
	`mu=((bet0)+(female)+(lnage)+(lnagefem)+(lnsbp)+(cig)+(lntchdl)+(dbetes)+(dbetesfem)+(ecg_lvh));`
	
	`sigma=exp(theta0+(theta1*mu));`
	
	`u=(log(5)-mu{i}/sigma);`
	
	`riskfram=(1-exp(-exp(u)));`

Framingham (10-year)	**Equation and variables needed** (Reproduced from D'Agostino et al, 2008) **Framingham (2008) risk equation:** $\hat{p} = 1 - S_0(t)^{exp(\sum_{i=1}^{p} \beta_i X_i - \sum_{i=1}^{p} \beta_i \bar{X}_i)}$

β and θ constant values and variables needed:

Coefficients	Constants (Female)	Constants (Male)
$S_0(10)$	0.95012	0.88936
Estimate from Framingham study population	26.9653	24.3509
log(age)	2.32888	3.06117
log(total cholesterol)	1.20904	1.12370
log(HDL cholesterol)	-0.70833	-0.93263
log(nontreated SBP)	2.76157	1.93303
log(treated SBP)	2.82263	1.99881
Smoker	0.52873	0.65451
Diabetes	0.69154	0.57367

Notes on equation set up:
The equation is set up separately for men and women.
SBP is entered in mmHg, Total and HDL cholesterol in mg/dl.

SAS code

(A Schultze, Oct. 2015)

```
/*Variables used:
gender=gender(1=male, 2=female)
rcurrage=age in years
rbp=systolic blood pressure
rhdl=hdl cholesterol
rch=total cholesterol
rdia=diabetes (1=yes, 0=No);
lvh=ECG left ventricular hypertrophy
rhyp=on antihypertensive drugs (1=yes)
*/

*women;
if gender=2 then do;

wage=2.32888*(log(rcurrage));
wtch=1.20904*(log(frch));
whch=(-0.70833)*(log(frhdl));
if rhyp ne 1 then do;
wsbpt=2.76157*(log(rbp));
end;
if rhyp=1 then do;
wsbpt=2.82263*(log(rbp));
end;
wsm=0.52873*risksmok;
wdb=0.69154*rdia;
```

```
wsum=wage+wtch+whch+wsbpt+wsm+wdb;

up_frisk=1-(0.95012**(exp(wsum-26.1931)));

end;

*men;
if gender=1 then do;

mage=3.06117*(log(rcurrage));
mtch=1.12370*(log(frch));
mhch=(-0.93263)*(log(frhdl));
if rhyp ne 1 then do;
msbpt=1.93303*(log(rbp));
end;
if rhyp=1 then do;
msbpt=1.99881*(log(rbp));
end;
msm=0.65451*risksmok;
mdb=0.57367*rdia;

msum=mage+mtch+mhch+msbpt+msm+mdb;

up_frisk=1-(0.88936**(exp(msum-23.9802)));
```

D:A:D Risk Equation (5-year)

Equation and variables needed
(Reproduced from Friis-Moller et al, 2010)

DAD risk equation:

$$1 - exp^{(-H \cdot t)}$$
$$where\ H = exp^{\beta_0+\beta_1 x_1+\beta_2 x_2+\beta_3 x_3+\beta_4 x_4+\beta_5 x_5+\beta_6 x_6+\beta_7 x_7+\beta_8 x_8+\beta_9 x_9+\beta_{10} x_{10}+\beta_{11} x_{11}+\beta+\beta_{12} x_{12}}$$

β constant values **(in red) and variables needed:**

	CVD	CHD	MI	Covariate, *x*
β_0	−10.970	−11.014	−11.695	
β_1	0.041	0	0.069	Multiply by duration of indinavir in years
β_2	0.077	0.074	0.111	Multiply by duration of lopinavir in years
β_3	0.489	0.547	0.715	β value if receiving abacavir, 0 otherwise
β_4	0.530	0.563	0.660	β value if male, 0 if female
β_5	0.348	0.342	0.291	β value times age/5
β_6	0.361	0.439	0	β value if family CVD history,0 otherwise
β_7	0.854	1.024	1.390	β value if current smoker, 0 otherwise
β_8	0.238	0.481	0.697	β value if ex-smoker, 0 otherwise
β_9	0.652	0.654	0.826	β value if diabetes, 0 otherwise
β_{10}	0.195	0.219	0.246	multiply by cholesterol (mmol/l)
β_{11}	−0.402	−0.518	−0.415	multiply by HDL (mmol/l)
β_{12}	0.054	0.035	0.039	multiply by systolic blood pressure/10

CHD, coronary heart disease; CVD, cardiovascular disease; HDL, high-density lipoprotein; MI, myocardial infarction.

Notes on equation set up:
"Data in the DAD study are set up in monthly time units (0.085 years); the above equation therefore produces a monthly probability of developing CVD, CHD or MI. A reasonably good approximation for calculating the estimated probability over longer time periods, *t*, is to multiply '*H*' by *t* years, and use indinavir + *t*/2 (if continuing on indinavir), lopinavir + *t*/2 (if continuing lopinavir) and age + *t*/2 in the equation."
(Appendix, Friis-Moller et al, 2010)

SAS code

(A Schultze, Oct. 2015)

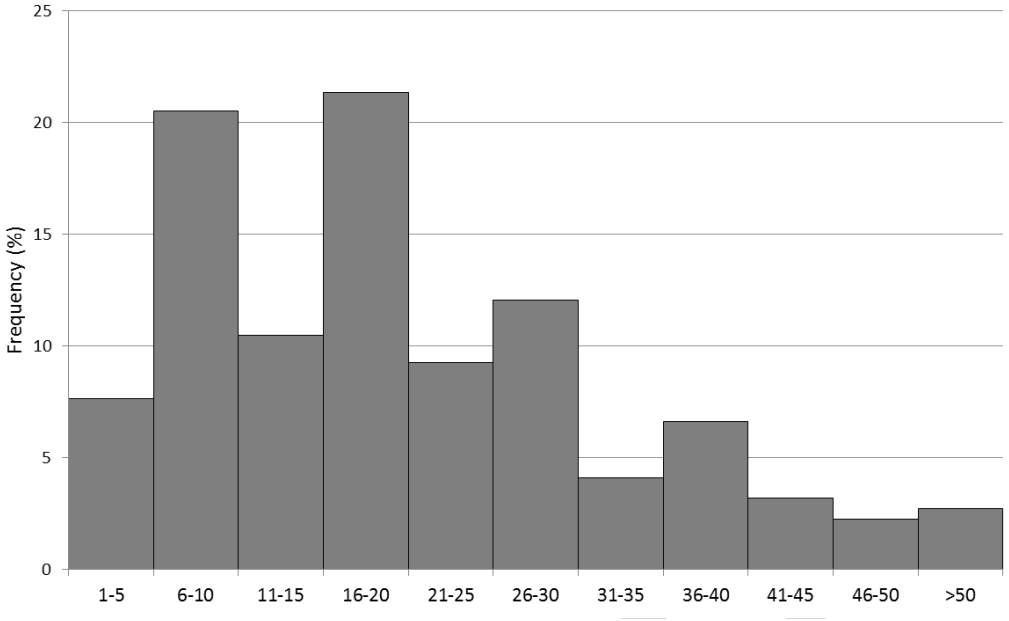
```
/*Variables used:
sumind=Cumulative exposure to indinavir
sumlop=Cumulative exposure to lopinavir
riskaba=On Abacavir (Yes=1, No=0)
riskgend=Gender(Male=1, Female=0)
rcurrage=Current age in years
famhist=Family history of CVD (Yes=1, No=0)
risksmok=Current smoker (Yes=1, No=0)
texsmok=Ex smoker (Yes=1, No=0)
rdia=Current Diabetes (Yes=1, No=0)
rch=LDL Cholesterol
rhdl=HDL Cholesterol
rbp=Blood Pressure

*/

*please note this is set up using absolute values, and minus signs added at the summation stage;
beta0=10.970;

if ind=1 then do;
bet1a=0.041*(sumind+(5/2));
end;
if ind=0 then do;
bet1a=0.041*(sumind);
end;

if lop=1 then do;
bet2a=0.077*(sumlop+(5/2));
end;
if lop=0 then do;
bet2a=0.077*(sumlop);
end;

bet3a=(0.489*riskaba);
bet4a=0.530*riskgend;
bet5a=0.348*(((rcurrage+(5/2))/5));
bet6a=0.361*famhist;
bet7a=0.854*risksmok;
```

	bet8a=0.238*texsmok;
	bet9a=0.652*rdia;
	bet10a=0.195*rch;
	bet11a=0.402*rhdl;
	bet12a=0.054*(rbp/10);
	sumrisk=((-beta0)+ bet1a + bet2a + bet3a + bet4a + bet5a + bet6a + bet7a + bet8a + bet9a + bet10a + (-bet11a) + bet12a);
	
	*this exponentiation stage is in accordance with the equation, but differs from the worked example in the Friis-Moller paper, due to an error (Matthew Law, pers. comm);
	riskex=(exp(sumrisk));
	
	fiveyear=5*(riskex);
	
	risk=(1-exp(-fiveyear));

1. For simplicity, the code is displayed without arrays. In the analysis, the risk equations were calculated on a monthly time-scale.

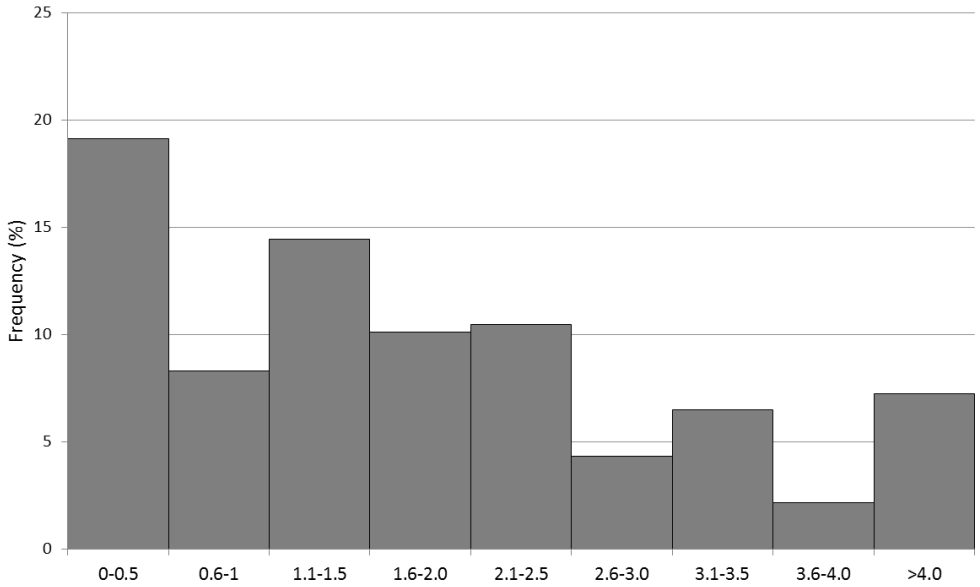
Appendix Figure 1a-b: Distribution of the magnitude of blood pressure/cholesterol modification

Figure 1a. Distribution of the magnitude of systolic blood pressure reduction (mm/Hg)[1,2]



1. For example, an individual with a BP of 150/90 who lowered their BP to 130/80 would be classified as having modified their SBP with 20 mm/Hg.
2. 131 individuals did not lower their systolic blood pressure but were still classified as having modified their blood pressure, as they met the EACS guidelines for indication for risk modification on the basis of their diastolic blood pressure values.

Figure 1b. Distribution of the magnitude of cholesterol reduction (mmol/Litre)[1]



1. 48 individuals did not lower their cholesterol as compared to their baseline cholesterol, as indication for modification of cholesterol was based on CV risk and not on absolute cholesterol values (Table 1). This meant that some individuals could meet the definition for successful cholesterol modification without a relative decrease in their cholesterol levels.