

ORIGINAL RESEARCH

Prevalence of risk factors for cardiovascular disease in HIV-infected patients over time: the Swiss HIV Cohort Study

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Objective

Metabolic changes caused by antiretroviral therapy (ART) may increase the risk of coronary heart disease (CHD). We evaluated changes in the prevalence of cardiovascular risk factors (CVRFs) and 10-year risk of CHD in a large cohort of HIV-infected individuals.

Methods

All individuals from the Swiss HIV Cohort Study (SHCS) who completed at least one CVRF questionnaire and for whom laboratory data were available for the period February 2000 to February 2006 were included in the analysis. The presence of a risk factor was determined using cut-offs based on the guidelines of the National Cholesterol Education Program (NCEP ATP III), the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7), the American Diabetes Association, and the Swiss Society for Cardiology.

Results

Overall, 8033 individuals completed at least one CVRF questionnaire. The most common CVRFs in the first completed questionnaire were smoking (57.0%), low high-density lipoprotein (HDL) cholesterol (37.2%), high triglycerides (35.7%), and high blood pressure (26.1%). In total, 2.7 and 13.8% of patients were categorized as being at high (>20%) and moderate (10–20%) 10-year risk for CHD, respectively. Over 6 years the percentage of smokers decreased from 61.4 to 47.6% and the percentage of individuals with total cholesterol >6.2 mmol/L decreased from 21.1 to 12.3%. The prevalence of CVRFs and CHD risk was higher in patients currently on ART than in either pretreated or ART-naïve patients.

Conclusion

During the 6-year observation period, the prevalence of CVRFs remains high in the SHCS. Time trends indicate a decrease in the percentage of smokers and individuals with high cholesterol.

Keywords: cardiovascular diseases, cardiovascular risk factors, highly active antiretroviral therapy, HIV infection, prevalence, time trends

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Introduction

There is growing evidence that HIV-infected individuals receiving antiretroviral therapy (ART) are at increased risk

of coronary heart disease (CHD) through increased incidence of dyslipidaemia, insulin resistance, and type 2 diabetes [1]. This increase in risk is mainly related to exposure to protease inhibitors (PIs) [2]. The association between exposure to ART and increased risk of myocardial infarction has been confirmed in several [3–5] but not all [6,7] studies. Although HIV infection affects younger populations generally at lower risk of CHD, almost 25%

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Table 1 Definitions of risk factors for cardiovascular diseases

Dyslipidaemia	Total cholesterol >6.2 mmol/L, HDL cholesterol <1.03 mmol/L, or fasting triglycerides >2.0 mmol/L
Hypertension	Systolic blood pressure \geq 140 mmHg and/or diastolic blood pressure \geq 90 mmHg (\geq 135/ \geq 85 mmHg in diabetic patients) or taking antihypertensive drugs
Diabetes	Definitive diagnosis, fasting plasma glucose \geq 7 mmol/L, casual plasma glucose >11.1 mmol/L, or taking antidiabetic drugs or insulin
Metabolic syndrome	Having any three of the following conditions: abdominal obesity (waist circumference >102 cm in men, >88 cm in women), triglycerides \geq 1.69 mmol/L, low HDL cholesterol (<1.03 mmol/L in men, <1.29 mmol/L in women), blood pressure \geq 130/ \geq 85 mmHg or diabetes
Family history for coronary heart disease	Myocardial infarction or stroke before the age of 50 years in any first-degree relative
Obesity	Body mass index (BMI) >30 kg/m ²

HDL, high-density lipoprotein.

of HIV-infected populations from several European and North American cohorts are at an age where there is an appreciable risk of CHD [8]. In a gender- and age-matched study, the prevalence of 10-year CHD risk in patients on ART was double the risk in HIV-negative controls [9]. Thus, a marked increase in CHD among HIV-infected patients is possible within the next decade as a result of prolonged survival and exposure to antiretroviral drugs.

Several studies have investigated the prevalence of risk factors for CHD in HIV-infected individuals [8,10,11]. However, there is little data available from well-defined populations on time trends in risk factors for CHD. Such information is important for a better understanding of the population-based risk for CHD over time in HIV-infected individuals who receive ART for many years. This study provides population-based estimates of the prevalence of cardiovascular risk factors (CVRFs) and the 10-year risk of CHD in the Swiss HIV Cohort Study (SHCS) over a period of 6 years.

Methods

Patients

The SHCS is a prospective cohort study with continuing enrolment of HIV-infected individuals aged \geq 16 years. After a 2-month pilot phase, a cardiovascular questionnaire was introduced into the regular follow up of the cohort on 1 April 2000. Visits take place every 6 months at seven out-patient clinics or specialized private practices and questionnaires are completed by clinicians and/or study nurses at the centres. All HIV-infected individuals who completed at least one CVRF questionnaire between 1 February 2000 and 26 February 2006 and had corresponding laboratory measurements within 30 days of the questionnaire were included in the analysis.

The questionnaire assesses the occurrence of any cardiovascular event, percutaneous coronary intervention or bypass surgery, family history of CHD, smoking status and lipodystrophy (judged by both patient and clinician).

Clinical examinations include a single office blood pressure, body weight and waist/hip ratio. Laboratory measurements taken at each visit (not necessarily in the fasting state) include blood glucose, total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, and triglycerides (TG).

Risk factors for CHD

The presence of a risk factor was determined using cut-offs based on guidelines of the National Cholesterol Education Program (NCEP ATP III) [12], the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) [13], the American Diabetes Association (ADA) [14], and the Swiss Society for Cardiology [15]. The definition and cut-offs for CVRFs are provided in Table 1. In addition, patients were considered to have a history of CHD if they had one of the following events: definite myocardial infarction, possible myocardial infarction or unstable angina, coronary artery bypass grafting, or coronary angioplasty or stenting. We defined coronary risk equivalents as the presence of cerebral infarction, carotid endarterectomy, procedures on other arteries, diabetes, or a Framingham 10-year risk >20% (with no history of CHD). An individual was considered to have stopped smoking if he/she admitted to smoking on a questionnaire but denied smoking on all subsequent questionnaires. At a minimum, smoking cessation had to be documented on at least two subsequent questionnaires at least 1 year apart. Therefore, cessation rates could not yet be estimated for visits in 2005 and 2006.

Antiretroviral treatment

Individuals were categorized according to ART treatment. Because lipid changes generally occur after 4 weeks but peak after 3 months of treatment with PI-based ART, we used the following definitions [16]. Anyone receiving ART for <3 months was considered 'treatment naive'. Anyone receiving ART for \geq 3 months was considered 'currently treated'. Anyone not currently treated but previously

treated for ≥ 3 months was considered 'pretreated'. At each visit, currently treated patients were further divided into the following categories: PI-based ART [including triple class regimens containing PIs and nonnucleoside reverse transcriptase inhibitors (NNRTIs)], NNRTI-based ART, triple nucleoside reverse transcriptase inhibitor (NRTI) regimen with trizivir, and other ART (consisting mostly of triple NRTI regimens other than trizivir, PI monotherapy or a boosted PI-based ART with one NRTI).

Statistics

The SHCS is an open cohort, and a population-based approach was utilized to evaluate the prevalence of and changes in CVRFs and CHD risk. Prevalence according to age and gender was estimated from the first questionnaire completed by an individual during the study period. At each subsequent questionnaire, patients were reclassified according to their treatment status at that time. For example, a naïve patient who began therapy between follow-up visits would be re-categorized as being currently treated if that patient had received more than 3 months of ART. The 10-year risk of CHD was calculated according to the point scoring system of the NCEP ATP III, which is based on an update of the Framingham database and methodology [12]. It utilizes gender, age, systolic blood pressure, TC, HDL cholesterol, and smoking status. Individuals were characterized as low (<10%), moderate (10–20%), or high risk (>20%) for developing CHD in 10 years. Changes in prevalence of CVRFs over time (overall and according to treatment status) were explored with summary tables and graphs divided into 6- or 12-month time periods. As the focus of this paper is a descriptive analysis of the prevalence in the cohort population, no formal testing and/or adjustment for confounders was performed. All analyses were performed with SAS 9.1 (SAS Institute, Cary, NC) and R version 2.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

There were 8186 individuals actively enrolled into the SHCS and 53854 questionnaires were completed between 1 February 2000 and 26 February 2006. Data from 8033 patients (98.1%) who completed at least one CVRF questionnaire during the study period and who had laboratory data within 30 days of the date of the questionnaire were included in the analysis. The percentage of missing data over all questionnaires with corresponding laboratory data was less than 4% for all derived CVRFs. The most frequently missing data were on metabolic syndrome (3.9%). In total, 20.8% of lipid measurements were made in the fasting state.

Prevalence of CVRFs

The prevalence of CVRFs from the first ever completed questionnaire is reported by sex and age groups: 69% were male and 43% of individuals were aged 40 years or older (Table 2). Of all first questionnaires, 63% were completed within 1 year after introduction of the questionnaire; the others were approximately equally distributed over the remaining 5 years of the observation period. The most common risk factor for cardiovascular disease was smoking, with a prevalence of 57%.

The percentage of individuals at moderate and high 10-year risk of CHD was 13.8 and 2.7%, respectively. Recalculation of this risk with the assumption that all smokers stopped smoking resulted in moderate and high 10-year risks of only 6.0 and 0.5%, respectively.

Changes in CVRFs and CHD risk over time

The number of patients under follow-up in the SHCS for the six 1-year time periods ranged from 5435 to 6149 (Table 3). Except for the first period (93%), >95% of these patients contributed at least one questionnaire and corresponding laboratory measurements to the respective time period. The average age increased from 40.1 to 43.4 years between 2000 and 2006. The most prominent changes over time were decreases in the percentage of smokers (from 61.4 to 47.6%) and the percentage of those with elevated TC (from 21.1 to 12.3%). We noted increases in the rates of diabetes (from 2.7 to 4.4%) and obesity (from 3.6 to 5.3%). The smoking cessation rate ranged from 2.9 to 5.1% of smokers stopping smoking in the different time periods.

Changes in lipid measurements and CHD risk over time according to ART

Between 3852 and 5189 patients contributed to the first 11 6-month time periods for the graphical analysis. Only 2428 patients contributed to the last time period as data collection for this time period is still ongoing. The population was divided by antiretroviral drug treatment status (naïve, pretreated or currently treated) and treated patients were further subdivided by type of ART at the time of the completed questionnaire. Currently treated patients were more often male and nonsmokers and, on average, were 2 years older than pretreated patients and 5 years older than naïve patients.

Changes in lipid levels according to treatment status are presented in Fig. 1. There was a steady decrease in the percentage of individuals with elevated TC, most prominently in the currently treated patients (Fig. 1a, left). Patients on PI-based ART and NNRTI-based ART had a

Table 2 Prevalence of cardiovascular risk factors (CVRFs) by age and gender*

Variable	Overall	Male		Female	
		< 40 years	≥ 40 years	< 40 years	≥ 40 years
Total [n (%)]	8033	2791 (35)	2757 (34)	1778 (22)	707 (9)
History of CHD (%) [†]	1.1	0.2	2.5	0.1	1.1
CHD risk equivalent (%) [‡]	5.8	3.7	11.9	1.0	3.4
Major CVRF (% of patients)					
Current smoker	57.0	64.3	52.5	53.9	53.4
Family history of CHD	12.0	11.2	3.1	10.2	14.6
Diabetes	2.7	1.6	5.1	0.8	2.2
Hypertension	26.1	24.4	36.0	11.6	30.3
Total cholesterol > 6.2 mmol/l	16.7	11.4	24.0	10.8	23.4
HDL-cholesterol < 1.03 mmol/l	37.2	45.6	43.0	21.1	22.3
Triglycerides					
> 2 mmol/l	35.7	34.5	46.7	21.4	32.8
Fasting value > 2 mmol/l [‡]	33.8	33.9	46.4	14.9	29.5
Obesity; BMI > 30 kg/m ²	3.9	2.4	4.1	4.9	6.4
Metabolic syndrome	15.0	12.3	21.4	7.7	19.4
Framingham 10-year risk of CHD [§]					
Moderate (10–20%)	13.8	8.0	32.1	0.6	4.2
High (> 20%)	2.7	1.4	6.4	0.1	0.3

*Data are taken from the first completed cardiovascular questionnaire between 1 February 2000 and 26 February 2006. For the definition of risk factors for cardiovascular disease, see Table 1.

[†]For definition, see Methods section.

[‡]Estimates based on patients with blood drawn in fasting state only.

[§]Calculated using the Framingham point scores as outlined in the NCEP ATP III guidelines [12]. For patients without a history of coronary heart disease (CHD), the point score predicts the risk of 'hard CHD', i.e. myocardial infarction or CHD death.

Table 3 Prevalence of cardiovascular risk factors (CVRFs) over time*

	Time period					
	2/2000– 3/2001	4/2001– 3/2002	4/2002– 3/2003	4/2003– 3/2004	4/2004– 3/2005	4/2005– 2/2006
Number of patients under follow-up [†]	5435	5463	5623	5837	6149	6119
Number of patients with CVRF questionnaire and laboratory data (% of total patients)	5049 (92.9)	5212 (95.4)	5414 (96.3)	5669 (97.1)	6046 (98.3)	5913 (96.6)
Age [mean (SD)]	40.1 (9.5)	40.9 (9.6)	41.6 (9.8)	42.2 (9.8)	42.8(10.0)	43.4(10.0)
History of CHD (%) [‡]	1.1	1.4	1.7	1.9	1.9	2.1
CHD risk equivalent (%) [‡]	6.8	7.0	7.5	7.4	7.6	7.3
Major CVRF (% of patients)						
Current smoker	61.4	56.0	54.2	51.2	49.5	47.6
Cessation rate (% of smokers) [‡]	5.1	3.1	4.4	2.9	–	–
Diabetes	2.7	3.4	4.0	4.3	4.2	4.4
Hypertension	27.0	27.3	28.4	26.8	29.8	29.4
Total cholesterol > 6.2 mmol/L	21.1	19.3	18.0	16.0	15.5	12.3
HDL-cholesterol < 1.03 mmol/L	34.9	36.1	36.0	36.7	36.8	30.9
Triglycerides > 2 mmol/L	40.3	40.0	39.5	38.0	36.8	36.9
Fasting value > 2 mmol/L [§]	37.4	38.8	39.1	36.3	38.0	34.6
Obesity; BMI > 30 kg/m ²	3.6	3.8	4.3	4.4	4.8	5.3
Metabolic syndrome (%)	15.8	17.5	17.9	17.1	17.4	16.6
Framingham 10-year risk of CHD [¶]						
Moderate (10–20%)	15.5	16.9	17.0	17.5	18.5	18.0
High (> 20%)	3.6	3.1	3.4	2.7	3.1	2.4

*Data are taken from the first completed cardiovascular questionnaire in each time period. For the definition of risk factors for cardiovascular disease, see Table 1. Note that family history of coronary heart disease (CHD) is only collected at the time of the first questionnaire and not updated. It is therefore omitted from this table.

[†]An individual was considered under follow up if he/she was registered and/or had at least one follow-up visit in the respective time period.

[‡]For definition, see Methods section.

[§]Estimates based on patients with blood drawn in fasting state only.

[¶]Calculated using the Framingham point scores as outlined in the NCEP ATP III guidelines [12] for patients without a history of CHD. The point score predicts the risk of 'hard CHD', i.e. myocardial infarction or CHD death.

SD, standard deviation.

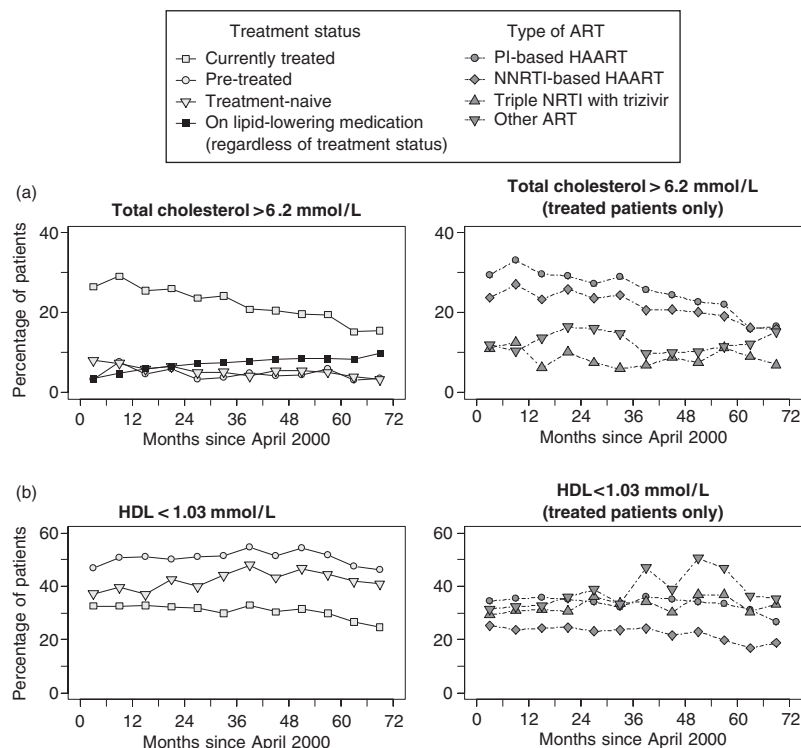


Fig. 1 Prevalence of cardiovascular risk factors over time by treatment status. (a) Total cholesterol > 6.2 mmol/L and use of lipid-lowering medication for all patients by treatment status (left) and for treated patients only by current antiretroviral therapy (ART) (right). (b) High-density lipoprotein (HDL) cholesterol < 1.03 mmol/L for all patients by treatment status (left) and for treated patients only by current ART (right).

consistently higher prevalence of elevated TC than patients on trizivir, although these differences were decreasing with time (Fig. 1a, right). There were no strong time trends in low HDL cholesterol. However, there were differences in the prevalence between treatment groups, namely a higher prevalence of elevated TC and a lower prevalence of low HDL cholesterol in currently treated patients. The percentage of individuals on lipid-lowering medications steadily increased from 3.5 to 9.8% (Fig. 1a, left).

Changes over time in Framingham risk scores are shown in Fig. 2. There were no strong time trends in the 10-year risk of CHD; however, as with the lipids, there were visible differences in the risk profile depending on treatment status. Although currently treated patients were more likely to be male and older, the higher risk in this subgroup persisted after stratifying by gender and age (data not shown).

Discussion

We found a high prevalence of CVRFs in HIV-infected individuals in the SHCS. In that respect, the SHCS is similar

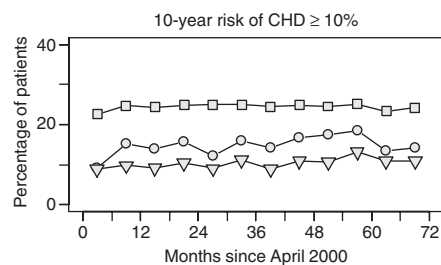


Fig. 2 Percentage of patients with Framingham 10-year risk of coronary heart disease (CHD) > 10% (according to the point scores as outlined in the NCEP ATP III [12]). Treatment status: squares, currently treated; circles, pretreated; triangles, treatment-naive.

to other HIV-infected populations, such as the multinational cohort study of Data Collection on Adverse Events of Anti-HIV Drugs (DAD) of which Swiss patients comprise 19.4% [8]. The 10-year risk of CHD in the SHCS is similar to that reported in HIV-infected cohorts in the USA, Australia and Spain [17,18]. The prevalence of risk factors and 10-year risk of CHD was mostly stable over time. It is possible that the decline in elevated TC in the currently treated group can be explained by an increase in those taking

lipid-lowering medications, although we could not draw a causal connection. The use of lipid-lowering medications almost tripled by 2005, implying that physicians are becoming aware of and responding to high rates of dyslipidaemia. Another explanation could be a greater use of NNRTI-based regimens. We saw increased prevalence of CVRFs and 10-year risk of CHD in those currently on ART, which was not entirely explained by differences in age or gender among the treatment groups.

The SHCS has an extremely high percentage of smokers, more than double that in the general Swiss population, although this decreased by 14% over the study period. The cessation rate of smokers ranged between 2.9 and 5.1% per year. Physicians should provide additional support to help patients successfully stop smoking, as it is an important and modifiable risk factor for CHD.

This study has several limitations. First, laboratory values were often not drawn in the fasting state, limiting the number of patients who could be accurately evaluated for TG and diabetes. However, Swiss treatment recommendations for hypercholesterolaemia are based on total cholesterol measurement. In addition, high blood pressure was based on a single office blood pressure measurement and it is likely that this led to an overestimate of prevalence and CHD risk. Smoking status was self-reported with no objective measure of carboxyhaemoglobin in those who indicated that they had stopped smoking. The Framingham algorithm was developed for the US population and may overestimate the CHD risk in HIV-infected populations and the Swiss population, which has a lower incidence of CHD events [19]. However, recent data suggest that the Framingham algorithm performs well in assessing risk of CHD in HIV-infected adults and that observed increases in risk of myocardial infarction could largely be explained by ART-induced changes in conventional CHD risk factors [20]. Finally, this study does not make any causal inferences on ART exposure and lipid changes, but such analyses from the SHCS have been provided elsewhere [21] or are the subject of ongoing research [22].

Despite these limitations, the SHCS is a large cohort with systematic data collection of CVRFs, making accurate estimation of changes in population prevalence over time possible. In addition, the response rate to the CVRF questionnaire was very high, suggesting that results are representative of the SHCS.

Our findings confirm the high prevalence of CVRFs and 10-year risk of CHD in HIV-infected patients and show differences by treatment status. Our study suggests that monitoring and management of CVRFs are gaining attention. We noted an increase in the prescription of lipid-lowering drugs and trends indicate a reduction of TC in patients receiving ART. However, CVRF management of

HIV-infected patients must be further improved. Monitoring of CVRFs in HIV-infected cohort studies must continue and intervention studies to improve CVRFs in HIV-infected patients at moderate to high risk of CHD should be introduced.

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