

CARDIOVASCULAR RISK FACTORS AND PROBABILITY FOR CARDIOVASCULAR EVENTS IN HIV-INFECTED PATIENTS:

PART II: GENDER DIFFERENCES*

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Abstract

Objective: Due to the side effects of antiretroviral therapy and long term survival there is an increasing concern of an elevated rate of cardiovascular diseases in HIV-infected patients. The present study analysed the cardiovascular risk profile and the probability of cardiovascular events in HIV-infected patients, due to differences of gender.

Methods: Cardiovascular risk factors of 309 HIV-infected adults, including 240 males were analysed. Overall 10-years probability for cardiovascular events was evaluated by the Framingham algorithm.

Results: Gender differences were detected in cardiovascular risk factors such as lipid values, blood pressure and the rate of smoking. Tobacco use was much more common in HIV-infected males compared with HIV-infected females (67.5% vs. 49.3%; $p < 0.001$). Although no significant difference was noticed in total cholesterol (5.49 ± 0.09 vs. 5.53 ± 0.19 mmol/L, $p = 0.84$), the HDL-cholesterol concentration was significantly lower (1.09 ± 0.03 vs. 1.36 ± 0.06 mmol/L, $p < 0.001$) and the triglyceride concentration higher (3.01 ± 0.21 vs. 2.06 ± 0.26 mmol/L, $p = 0.02$) in HIV-infected males compared to HIV-infected females. Additionally, systolic blood pressure was higher in HIV-infected males compared with HIV-infected females (123.1 ± 1.1 vs. 115.4 ± 2.1 mmHg, $p < 0.01$). No significant differences were detected in HbA1c - concentrations between both groups (5.15 ± 0.07 vs. 5.31 ± 0.11 , $p = 0.26$). The overall 10-years probability for cardiovascular events was 8.7% (me-

dian) in HIV-infected males and 1.7% in HIV-infected females ($p < 0.0001$).

Conclusions: In the present study, we observed gender differences in the cardiovascular risk profile of HIV-infected individuals. The risk of premature atherosclerosis and associated cardiovascular events was significantly higher in HIV-infected males.

Key words: HIV; gender; cardiovascular risk factors; arteriosclerosis

INTRODUCTION

Since the development of new effective antiretroviral therapy concepts (HAART) and the associated long term survival of HIV-infected patients, an increasing rate of cardiac manifestations has been described (Detels et al. 1998, Detels et al. 2001, Fisher et al. 2001, Palella et al. 1998, Periard et al. 1999). Especially, concerns about HIV-associated coronary heart disease have been risen because of an increasing rate of atherosclerosis in HIV-infected patients and a significantly higher rate of coronary heart disease compared to non-infected individuals (Morgello et al. 2002, Klein et al. 2003).

As previously described by our group, HIV-infected patients exhibit an elevated cardiovascular risk profile (Neumann et al. 2003). In contrast to previous assumptions, the increased cardiovascular risk profile did not primarily depend on an elevated rate of HAART associated risk factors such as the total cholesterol and triglyceride levels. However, HIV-positive patients also exhibit an extension of cardiovascular risk factors which are not influenced by HAART. In particular, increased age and a higher amount of smoked cigarettes increase the possibility of coronary artery disease in HIV-infected patients. In addition, gender ratio in

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the HIV-infected population seemed to have a remarkable impact on the rate of cardiovascular events.

Until now, the reasons for premature arteriosclerosis in HIV-infected subjects have not been described in detail and alterations in the cardiovascular risk profile between subgroups of HIV-infected individuals are still unknown. The aim of the present study was (1) to characterize gender differences in cardiovascular risk factors, effected and unaffected by HAART, and (2) to determine the risk of cardiovascular events in male and female HIV-infected patients.

MATERIALS AND METHODS

PATIENTS

All HIV-infected individuals who attended the internal medical department of the University of Essen between March 1997 and March 2002 were included in the present study. Demographic data, state of infection, and antiretroviral medication of each patient were considered for analysis. In addition, each subject was interviewed for cardiovascular risk factors including personal history, lipid disorders, and smoking behaviour. If subjects were smokers, further information including the amount of cigarettes per day as well as the frequency and the overall time period of smoking - resulting in pack years data - were recorded. In all patients, a physical examination was performed. In addition, venous blood samples were obtained for further analysis. Resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by oscillometric sphygmomanometry. Patients with HAART for less than four consecutive weeks were excluded. Nine percent ($n = 29$) of the patients were on lipid-lowering therapy. Therefore, in these patients, lipid values before initiation of lipid lowering therapy were taken for the analysis.

LABORATORY METHODS

Venous blood (10 ml) was collected into serum specimen tubes and centrifuged at 2000 rpm for 15 minutes. A 1.0 ml aliquot was withdrawn, and total cholesterol, HDL cholesterol (HDL-C), LDL-cholesterol (LDL-C), triglyceride levels, glucose and HbA1C were measured by enzymatic methods on Bayer ADVIA1650 analyser with standard reagents. The cholesterol method (Bayer Diagnostics) is based on an enzymatic method utilising cholesterol esterase and cholesterol oxidase conversion followed by a Trinder endpoint. The triglyceride method (Bayer Diagnostic) is based on the Fossati three-step enzymatic reaction with a Trinder endpoint. The single reagent procedure quantitates the total triglyceride including the mono- and diglycerides and the free glycerol fractions. The Direct-High-Density Lipoprotein method (Greiner Biochemica) measures HDL-cholesterol without prior separation, using polyethy-

lene glycol (PEG) modified enzymes. The Direct-Low-Density Lipoprotein method (Greiner Biochemica) measures LDL-Cholesterol without prior separation using detergents and cholesterol-esterase and cholesterol-oxidase followed by a Trinder endpoint. The glucose method (Bayer Diagnostics) is based on the method by Slein utilising hexokinase and glucose-6-phosphatase dehydrogenase enzymes. The HbA1c method (Bayer Diagnostics) is based on a latex agglutination inhibition assay. For virus load and CD4-count 5 ml blood was collected into EDTA specimen tubes. The CD4 cell counts were determined by flow cytometry. Plasma HIV RNA titres were measured by b-DNA hybridisation assay. Lower detection value for virus load was 50 copies per ml.

CALCULATION OF CORONARY HEART DISEASE RISK

The prediction of coronary heart disease was performed based on the Framingham algorithm (Wilson et al. Circ 1998). Age, gender, total cholesterol, LDL cholesterol, blood pressure, smoking and diabetes were considered as major cardiovascular risk factor in the calculation. The result of the Framingham prediction algorithm determines the 10-year probability of coronary heart disease.

STATISTICAL ANALYSIS

All data are expressed as mean value \pm SEM. The comparison of these variables was performed between two distinct groups using one-way ANOVA and t-test analysis as post-hoc procedure. Nominal variables, including the rate of smoking, were expressed as frequencies; the comparison between distinct groups was performed using Chi-square test. Skewed variables such as variables describing the probability of coronary events were expressed as median (lower quartile, upper quartile); the comparison between distinct groups was performed by Dunn's test as posthoc analysis. A difference was considered significant at $p < 0.05$.

RESULTS

CLINICAL CHARACTERISTICS

In total, cardiovascular risk factors of 309 HIV-infected adults, including 240 males were analysed in the present study. Of all patients 183 (59.2%) revealed HIV-infection by man having sex with man, 88 (28.5%) by heterosexual contact, 28 (9.1%) acquired HIV-infection by intravenous drug use (IVDU) and 10 (3.2%) by blood transfusion. This distribution is representative for HIV-infected patients in most industrial countries.

Demographic data of all analysed patients are presented in Table 1. HIV-infected males were significantly older than HIV-infected females, possibly due to different time points of HIV acquisi-

Table 1. Clinical characteristics of HIV-infected individuals.

	All	Males	Females	p - value
N	309	240	69	
Age, y	42.1 ± 0.7	42.6 ± 0.7	37.3 ± 1.1	< 0.001
Height, cm	175.1 ± 0.5	178.0 ± 0.5	164.2 ± 0.9	< 0.001
Weight, kg	70.4 ± 0.8	72.3 ± 0.9	64.0 ± 1.3	< 0.001
BMI, kg/m ²	22.9 ± 0.2	22.7 ± 0.2	23.7 ± 0.5	0.07
HIV-RNA copies / ml	15,013 ± 2,357	13,929 ± 2,139	18,792 ± 7,476	0.39
CD4 cells / mm ³	454 ± 16	458 ± 18	441 ± 33	0.67

Demographic data are presented as mean values ± SEM

Table 2. Cardiovascular risk factors influenced by HAART.

	All	Male	Female	p - value
Total cholesterol, mmol/L	5.50 ± 0.08	5.49 ± 0.09	5.53 ± 0.19	0.84
HDL-cholesterol, mmol/L	1.15 ± 0.03	1.09 ± 0.03	1.36 ± 0.06	< 0.001
LDL-cholesterol, mmol/L	3.49 ± 0.08	3.50 ± 0.09	3.47 ± 0.19	0.88
Triglycerides, mmol/L	2.80 ± 0.17	3.01 ± 0.21	2.06 ± 0.26	0.02
Glucose, mmol/L	5.90 ± 0.10	6.03 ± 0.12	5.47 ± 0.14	0.02
HbA1c, %	5.19 ± 0.06	5.15 ± 0.07	5.31 ± 0.11	0.26

Data are mean values ± SEM; HDL: high density lipoprotein; LDL: low density lipoprotein.

tion. Additionally, HIV-infected males were taller and had a higher body weight than HIV-infected females. However, body mass index was not significantly different between both groups. As well, there were no significant differences in HIV-RNA copies and CD4-cell count between both groups.

The clinical staging of the disease was similar in both groups. Overall, 31.5% of the patients being in CDC stage C, 32.5% in CDC stage B and, respectively, 36.1% in CDC stage A. No statistically significant differences were noticed between groups in respect to therapy of PIs, non-nucleoside reverse transcriptase inhibitors (NNRTIs) and nucleosidal reverse transcriptase inhibitors (NRTIs).

Gender differences were detected in cardiovascular risk factors both influenced as well as not influenced by antiretroviral medication:

CARDIOVASCULAR RISK FACTORS BEING INFLUENCED BY ANTIRETROVIRAL MEDICATION (Table 2)

According to the guidelines of the European atherosclerosis society, the mean plasma level of cholesterol was borderline in both analysed groups. However, in 56.7% of HIV-infected males and in 56.5% of HIV-infected females the cholesterol

level was increased (> 5.2 mmol/l). As previously described, an exponential increase of coronary artery disease is present in patients with a total cholesterol level over 6.2 mmol/l (Assmann et al. Am J Cardiol 1996). A total cholesterol level of more than 6.2 mmol/l was determined in 27.5% and 29.0% of HIV-infected males and females, respectively.

Plasma levels of HDL- and LDL-cholesterol of all analysed HIV-infected patients were in the physiological range according to the guidelines of the European atherosclerosis society. While there was no significant difference between both groups for LDL-cholesterol, HDL-cholesterol was significantly lower in HIV-infected males ($p < 0.001$).

The mean triglyceride plasma concentration, however, was increased in HIV-infected patients. Particularly high triglyceride plasma concentrations were found in HIV-infected males (Table 2). While 44.6% of all HIV-infected males showed triglyceride concentrations that were higher than the physiological upper limit of 2.3 mmol/L, the rate of elevated triglyceride concentration in HIV-infected females was 24.6% ($p < 0.01$).

Further analysed cardiovascular risk factors being presented in Table 2 did not differ significantly between both groups. Although there had been an increased glucose concentration in HIV-

Table 3. Cardiovascular risk factors non-influenced by HAART.

	All	Male	Female	p - value
Smoking, %	63.4%	67.5%	49.3%	< 0.01
- package-years	21.8 ± 1.1	22.5 ± 1.2	18.6 ± 2.9	0.18
- cigarettes per day	24.9 ± 1.0	25.1 ± 1.1	23.9 ± 2.7	0.66
systolic BP, mmHg	121.4 ± 1.0	123.1 ± 1.1	115.4 ± 2.1	< 0.01
diastolic BP, mmHg	78.7 ± 0.7	79.4 ± 0.8	76.3 ± 1.4	0.06

Data are mean values ± SEM; BP: blood pressure

infected males, HbA1c did not differ significantly between the two groups. In addition, the rate of diabetes was not significantly increased in HIV-infected males.

CARDIOVASCULAR RISK FACTORS NOT BEING INFLUENCED BY ANTIRETROVIRAL MEDICATION (Table 3)

Overall, HIV-infected patients exhibited an increased tobacco use. About two-thirds of the HIV-infected patients were regular smoker (Table 3), nearly all of them consuming cigarettes (only one patient smoked pipe). Tobacco use was much more common in HIV-infected males than in females. However, between both groups there was no significant difference in the time interval of smoking and the amount of cigarettes consumed (pack-years, cigarettes per day). Only 3.8% of HIV-infected males and 1.4% of females showed a daily cigarette consumption that was less than 5 cigarettes. In contrast, 13.3% of males and 10.1% of females smoked more than 40 cigarettes each day.

A history of hypertension was present in 11.7% of HIV-infected males and in 5.8% of HIV-infected females. Overall, systolic and diastolic blood pressure values were not significantly elevated in both groups. Systolic blood pressure was lower in HIV-infected females. Systolic blood pressure >140 mmHg was observed in 18.8% of HIV-infected males and in 13.0% of HIV-infected females. Increased diastolic blood pressure >90 mmHg was present in 10.0% of male and in 5.8% of female patients.

PREDICTION OF CORONARY HEART DISEASE

The mean prediction value for manifestation of coronary heart disease during the next 10 years was 7.0% (median) in all HIV-infected patients. As expected from the differences in cardiovascular risk factors between the gender groups, there was a significant discrepancy between male and female patients (Fig. 1). The overall risk for coronary heart disease during the next 10 years was significantly higher for male HIV-infected subjects than for females ($p < 0.0001$).

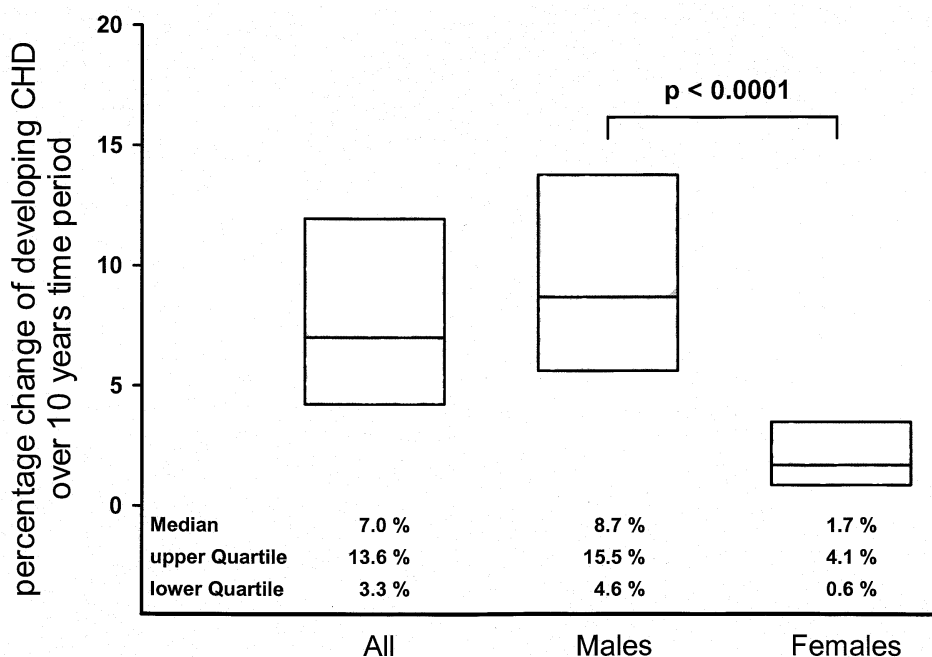


Fig. 1. The 10-year probability for coronary heart disease determined by the Framingham prediction algorithm. The 10-years probability for cardiovascular events is significantly higher in HIV-infected males compared with HIV-infected females. Data are expressed as median plus lower quartile and upper quartile.

DISCUSSION

Major finding of the present study are the various differences in cardiovascular risk factors between HIV-infected males and females. These differences did not only include HAART associated cardiovascular risk factors such as LDL-cholesterol and triglyceride levels. Gender differences were also present in cardiovascular risk factors not being influenced by HAART. The importance of these findings is emphasized by a significant discrepancy between the probability of cardiovascular events in HIV-infected males and females.

Concerns about an increase of HIV-associated coronary heart disease rose because of the side effects of new antiretroviral drugs (Fischer et al. 2001). However, at present there are only preliminary data concerning cardiovascular risk factors and cardiovascular events in HIV-infected patients and the potential role of antiretroviral therapy. One of the largest epidemiological studies observed a slight decline in cardiovascular and cerebrovascular events in HIV-infected patients during the last years; nevertheless, the rate of death due to cardiovascular and cerebrovascular events increased in this patient population (Bozzette et al. 2002). Further analysis of hospitalisation rate for coronary heart disease and myocardial infarction also reported no significant effect of HAART (Klein et al. 2002). However, HIV-infected patients presented a significantly higher rate of cardiovascular events compared to noninfected subjects. This lack of a relation between HAART and the incidence of cardiovascular events emphasises the assumption that other risk factors may be responsible for the premature atherosclerosis observed in HIV-infected patients.

In a previous study, we demonstrated an elevated cardiovascular risk profile in HIV-infected patients (Neumann et al. 2003). Especially cardiovascular risk factors that were not influenced by HAART, such as gender, age and smoking, were significantly increased. The elevated rate of male subjects in this population seemed to be one of the major reasons for the increased probability of cardiovascular events. However, in the present study we could demonstrate that HIV-infected males also have an increased cardiovascular risk profile by themselves.

This increased risk profile of HIV-infected males results mainly from risk factors which are not influenced by HAART such as an increased age, a slightly higher systolic blood pressure and an elevated rate of smoking. An increased age of HIV-infected patients had been observed in previous studies (Stein et al. 2001). The rate of male patients in combination with the elevated age might increase the probability of cardiovascular events. In addition, major concerns for cardiovascular events in HIV-infected males result from the elevated smoking rate. The federal statistic bureau observed in residents of the same area a regular smoking rate of 25.5%, however, the smoking rate in HIV-infected males was 67.5% (Stat. Bundesamt

2002). Moreover, the daily cigarette consumption of non HIV-infected smokers was less (16.4 vs. 24.9 cigarettes per day).

Although large published series of HIV-infected patients being treated with protease inhibitors support an increase of total cholesterol, we did not see a lasting effect of this HAART-influenced cardiovascular risk factor in the present study (Behrens et al. 1999 ; Carr et al. 1998; Periard et al. 1999 ; Walli et al. 1998).

In summary, it can be assumed that the rate of cardiovascular events in HIV-infected individuals will rise in the near future, especially in HIV-infected males. While premature atherosclerosis had been detected already before the HAART era, the increase in life expectancy of HIV-infected patients by the implication of HAART will increase the impact of cardiovascular risk factors in HIV-infected patients. Especially, HIV-infected males exhibit an increased profile of both cardiovascular risk factors being influenced by HAART and classic cardiovascular risk factors not being influenced by HAART. Our findings may contribute to the development of new concepts for the prevention of cardiovascular events in HIV-infected patients.

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