Eur J Med Res (2004) 9: 267-272

Cardiovascular Risk Factors and Probability for Cardiovascular Events in HIV-Infected Patients

Part III: Age Differences*

T. Neumann[1], T. Woiwod[1], A. Neumann[2], M. Miller[3], C. von Birgelen[1, 4], L. Volbracht[5], S. Esser[6], N. Brockmeyer[7], G. Gerken[3], R. Erbel[1]

[1]Department of Cardiology, University of Duisburg-Essen, Medical School, Germany
[2]Alfried Krupp von Bohlen und Halbach Foundation-Institute for Health Systems Management, University of Duisburg-Essen, Germany
[3]Department of Cardiology, Medish Spectrum Twente, Enschede, The Netherlands
[4]Department of Gastroenterology, University of Duisburg-Essen, Medical School, Germany
[5]Department of Clinical Chemistry, University of Duisburg-Essen, Medical School, Germany
[6]Department of Dermatology, University of Duisburg-Essen, Medical School, Germany
[7]Department of Dermatology, University of Bochum, Medical School, Germany

Abstract

Objective: In recent years, concerns have been growing about an elevated rate of cardiovascular diseases in HIV-infected patients due to side effects of antiretroviral therapy. The present study analyses the cardiovascular risk profile and the probability of cardiovascular events with regard to the age of HIV-infected patients.

Methods: Cardiovascular risk factors of 309 HIV-infected adults were analysed. Patients were divided into four groups: 18-30 years (group 1), 31-40 years (group 2), 41-50 years (group 3), > 50 years (group 4). Overall 10-years probability for cardiovascular events was evaluated by the Framingham algorithm.

Results: Differences between the groups were detected in cardiovascular risk factors including changes in lipid- and glucose metabolism. Lipid values increased with elevated age, such as total cholesterol concentration (group 1 vs. group 4: 4.71 ± 0.20 to 6.36 ± 0.21 mmol/L, $p < 0.05$), LDL-cholesterol concentration (2.86 ± 0.17 vs. 4.17 ± 0.21 mmol/L, $p < 0.05$) and triglyceride concentration (1.56 ± 0.14 vs. 3.48 ± 0.40 mmol/L, $p < 0.05$). HDL-cholesterol concentration (Mean ± SEM: 1.15 ± 0.03 mmol/L) did not show a significant different. Glucose concentration increased with elevated age in HIV-infected patients (5.28 ± 0.19 vs. 6.46 ± 0.24 mmHg, $p < 0.05$), but there was no significant difference in HbA1c – concentration, blood pressure and smoking rate between the groups. The overall 10-years probability for cardiovascular events was higher in group 1 (median: 1.9%) than in group 4 (20.5%; $p < 0.01$).

Conclusions: The risk of cardiovascular events is related to the age in HIV-infected patients. Therefore, an increased duration of life due to a more effective antiretroviral therapy will have a significant impact on the rate of cardiovascular events in this patient population. In the future, further increase of cardiovascular events in HIV-infected patients may be expected.

Key words: HIV, age, cardiovascular risk factors, arteriosclerosis

Introduction

The infection with the human immunodeficiency virus (HIV) is still one of the great challenges in medicine. Although new highly active antiretroviral medications (HAART) significantly reduced morbidity and mortality, an increasing rate of HIV-associated manifestation had been described (Detels et al. 1998, Detels et al. 2001, Fisher et al. 2001, Palella et al. 1998, Periard et al. 1999). In particular, an increased rate of premature atherosclerosis in HIV-infected patients and a higher rate of coronary events compared to non-infected individuals have rise to concerns about HIV-associated coronary heart disease (Morgello et al. 2002, Klein et al. 2003).

As previously described by our own group, HIV-infected patients exhibit an elevated cardiovascular risk profile (Neumann et al. 2003; Neumann et al. 2004). Surprisingly, the increased cardiovascular risk profile did not depend primarily on HAART associated risk factors such as total cholesterol and triglyceride levels, but on cardiovascular risk factors not being influenced by HAART, such as increased age and an elevated rate of smoking. In addition, the increased duration of live due to the new antiretroviral therapy might have a remarkable impact on the rate of cardiovascular events.

Until now, the effect of age on the cardiovascular risk profile and the risk of cardiovascular events have not been analysed in detail. The aim of the present study was to characterize age differences in cardio-

*The work is not supported in the form of sponsorship or any affiliations that might lead to bias or conflict of interest.

vascular risk factors - effected and unaffected by HAART - and to determine the risk of cardiovascular events in this patient population.

Materials and Methods

Patients

All HIV-infected individuals who were treated in the department of internal medicine of the University of Essen between March 1997 and March 2002 were divided into four groups: 18-30 years (group 1), 31-40 years (group 2), 41-50 years (group 3), > 50 years (group 4). Demographic data, state of infection, and antiretroviral medication of each patient were taken into analysis. In addition, each subject was questioned for cardiovascular risk factors including personal history, lipid disorders, and smoking behaviours. If subjects were smokers, further information including the number of cigarettes smoked per day as well as the frequency and the time period of smoking (resulting in pack years data) were recorded. All patients were physically examined, resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by oscillometric sphygmomanometry. Venous blood samples were obtained for further analysis. Patients with HAART, including a protease inhibitor, for less than four consecutive weeks were excluded. Nine percent (n = 29) of the patients were on lipid-lowering therapy; in these patients, lipid values before initiation of the lipid-lowering therapy were taken for 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 polyethylene glycol (PEG) modified enzymes. The Direct-Low-Density Lipoprotein method (Greiner Biochemica) measures LDL-Cholesterol without prior separation using detergents and cholesterinesterase and cholesteroloxidase 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 titre's 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 determined by the Framingham algorithm (Wilson et al. Circ 1998). The major cardiovascular risk factors age, gender, total cholesterol, LDL cholesterol, blood pressure, smoking and diabetes were considered in the calculation. The result of the Framingham prediction algorithm determines the 10-year probability of major coronary events.

Statistical Analysis

All data are expressed as mean value ± 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 exact 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 were analysed in the present study. Demographic data of all analysed patients are presented in Table 1. HIV-infected subjects in group 1 were significantly shorter than the subjects of the three other groups, but total body weight and body mass index did not differ significantly between groups. In addition, there were no significant differences in HIV-RNA copies and CD4-cell count between groups. 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 and 10 (3.2%) by blood transfusion. Further information on the for acquisition of HIV-infection, CDC-stage and antiretroviral therapy are presented in Table 2.

Cardiovascular Risk Factors Being Influenced by Antiretroviral Medication (Table 3)

Lipid values increased significantly with age. For example, the total cholesterol concentration displayed a stepwise increase from group 1 to group 4. While in group 1 only 34.4% of the subjects had a cholesterol level > 5.2 mmol/l, this rate increased up to 84.6% in group 4 (group 2: 42.2%; group 3: 64.0%). As previously described, an exponential increase of coronary

Table 1. Clinical characteristics of HIV-infected individuals.

	All	18-30	31-40	41-50	>50
N	309	32	121	89	67
Age, y	42.1 ± 0.7	27.1 ± 0.6	36.0 ± 0.1	45.0 ± 0.1	59.1 ± 0.1
			p<0.05		
Height, cm	175.1 ± 0.5	170.2 ± 1.9	176.9 ± 0.8	175.0 ± 1.0	174.2 ± 1.0
Weight, kg	70.4 ± 0.8	65.3 ± 1.8	71.3 ± 1.3	71.0 ± 1.3	70.6 ± 1.5
BMI, kg/m^2	22.9 ± 0.2	22.8 ± 0.6	22.6 ± 0.4	23.2 ± 0.4	23.2 ± 0.5
HIV-RNA, copies/ml	15,013 ± 2,357	24,369 ± 9,056	19,233 ± 4,956	13,521 ± 2,874	5,074 ± 1,821
CD4-Count, cells/mm^3	454 ± 16	456 ± 41	450 ± 27	458 ± 29	454 ± 36

Demographic data are presented as mean values ± SEM; significant differences ($p<0.05$) between two values are expressed by solid lines.

Table 2. HIV-acquisition, CDC-stage and antiretroviral therapy.

	18-30	31-40	41-50	>50
Acquisition of HIV-Infection		p < 0.05		
• homosexual contact	34.4%	60.3%	58.4%	70.1%
• heterosexual contact	56.3%	27.3%	28.1%	17.9%
• intravenous drug abuse	9.4%	10.7%	9.0%	6.0%
• blood transfusion	0.0%	1.7%	4.5%	6.0%
CDC-stage		p < 0.05		
• Stage A	56.3%	33.9%	30.3%	17.9%
• Stage B	34.4%	26.4%	32.6%	34.3%
• Stage C	9.4%	35.5%	37.1%	44.8%
Antiretroviral Therapy		p < 0.05		
• NRTI	71.9%	83.5%	86.5%	95.5%RTI
• NNRTI	37.5%	40.5%	36.0%	43.3%
• PI	21.9%	39.7%	50.6%	62.7%

Data are presented as percentage; significant differences ($p<0.05$) between two values are expressed by solid lines.

artery disease can been found in patients with a total cholesterol level over the threshold of 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 12.5%, 17.4%, 28.1% and 53.7% of HIV-infected subjects in groups 1 to 4, respectively.

Overall, mean plasma levels of HDL- and LDL-cholesterol were in the physiological range, according to the guidelines of the European athero-sclerosis society. LDL-cholesterol increased from groups 1 to 4 up to an elevated value of 4.17 mmol/l ($p<0.05$), while there was no significant difference between the groups for HDL-cholesterol.

Similar to total cholesterol levels, the triglyceride plasma concentration was also increased in HIV-infected patients. Particularly high triglyceride plasma concentrations were found in HIV-infected subjects in group 3 and 4. While in group 1 only 18.8% of all HIV-infected patients showed triglyceride concentrations higher than the physiological upper limit of 2.3 mmol/L, the rate of elevated triglyceride concentration increased up to 26.4%, 49.4% and 62.7% in groups 2, 3 and 4, respectively ($p<0.01$).

Despite changes in lipid parameters, there were also alterations in the glucose metabolism - the second HAART-influenced cardiovascular risk factor. Serum glucose concentration increased from 5.28 in group 1 up to 6.46 mmol/L in group 4. The HbA1c parameter was higher in group 4 (5.34%) compared with groups 1 and 2 (5.14%) (n.s.). In addition, the

Table 3. Cardiovascular risk factors influenced by HAART.

	All	18-30	31-40	41-50	>50
Total cholesterol, mmol/L	5.50 ± 0.08	4.71 ± 0.20	5.17 ± 0.11	5.58 ± 0.12	6.36 ± 0.21
HDL-cholesterol, mmol/L	1.15 ± 0.03	1.18 ± 0.07	1.19 ± 0.05	1.13 ± 0.05	1.10 ± 0.05
LDL-cholesterol, mmol/L	3.49 ± 0.08	2.86 ± 0.17	3.25 ± 0.11	3.55 ± 0.17	4.17 ± 0.21
Triglycerides, mmol/L	2.80 ± 0.17	1.56 ± 0.14	2.33 ± 0.25	3.36 ± 0.38	3.48 ± 0.40
Glucose, mmol/L	5.90 ± 0.10	5.28 ± 0.19	5.70 ± 0.17	5.99 ± 0.16	6.46 ± 0.24
HbA1c, %	5.19 ± 0.06	5.14 ± 0.17	5.14 ± 0.09	5.15 ± 0.09	5.34 ± 0.15

Data are mean values ± SEM; HDL: high density lipoprotein; LDL: low density lipoprotein; significant differences ($p<0.05$) between two values are expressed by solid lines.

Table 4. Cardiovascular risk factors non-influenced by HAART.

	All	18-30	31-40	41-50	>50
Smoking, %	63.4%	59.4%	63.6%	70.8%	55.2%
- package-years	21.8 ± 1.1	10.7 ± 1.4	17.6 ± 1.1	24.5 ± 2.0	31.7 ± 3.2
- cigarettes per day	24.9 ± 1.0	19.9 ± 1.7	24.1 ± 1.3	26.1 ± 1.9	26.9 ± 2.8
systolic BP, mm Hg	121.4 ± 1.0	116.8 ± 2.5	119.9 ± 1.7	121.3 ± 1.8	126.1 ± 2.2
diastolic BP, mm Hg	78.7 ± 0.7	76.0 ± 1.7	78.3 ± 1.2	79.3 ± 1.2	79.8 ± 1.5

Data are mean values ± SEM, except smoking rate (data presented as percentage); BP: blood pressure; significant differences ($p<0.05$) between two values are expressed by solid lines.

rate of patients with diabetes type II increased from 0% in group 1 to 10.4% in group 4.

Cardiovascular Risk Factors not Being Influenced by Antiretroviral Medication (Table 4)

Overall, HIV-infected patients exhibited an increased tobacco use. Nearly two-third of the HIV-infected patients were regular smokers. However, no significant differences were noticed between the analysed groups regarding the rate of smoking and daily tobacco consumption. While in all groups less than 5% of the patients had a daily cigarette consumption ≤ 5 cigarettes, the rate of smoking > 40 cigarettes daily varied from 3.1% in group 1 up to 19.1% in group 3 (group 2: 9.9%; group 4: 13.4%).

Systolic and diastolic blood pressure values were in a physiological range and did not differ significantly between the four groups. However, older HIV-infected patients exhibited a significantly higher rate of history of arterial hypertension (group 4: 20.9%, $p<0.05$). In addition, in this group a systolic blood pressure >140 mmHg was observed in 18.2% ($p<0.05$ v. group 1 (0.0%), group 2 (9.3%) and group 3 (9.4%)) and an increased diastolic blood pressure >90 mmHg in 12.1% ($p<0.05$ v. group 1 (0.0%) and group 2 (8.3%)).

Prediction of Coronary Heart Disease

Overall, the mean prediction value for manifestation of coronary heart disease during the next 10 years was 7.0% (median) in HIV-infected patients. As could be expected from the differences in cardiovascular risk factors between the groups, there was a significant increase of the overall 10-years probability of cardiovascular events with increasing age from 1.9% in group 1 up to 20.5% in group 4 (Fig. 1).

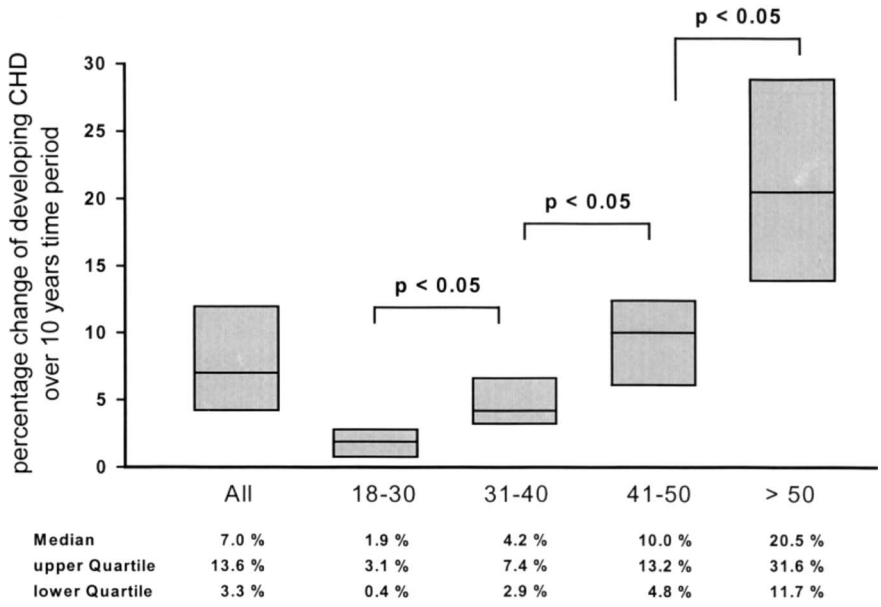

Fig. 1. The 10-year probability of coronary heart disease determined by the Framingham prediction algorithm. The risk of cardiovascular events is significantly related to the age in HIV-infected patients and increased from 1.9% (median) in younger HIV-positive subjects (group 1) up to 20.5% in older HIV-infected subjects (group 4). Data are expressed as median plus lower quartile and upper quartile.

Discussion

In the present study, we could demonstrate age differences of cardiovascular risk factors in HIV-infected patients. These differences primarily include HAART associated cardiovascular risk factors such as total cholesterol, LDL-cholesterol and triglyceride levels. The importance of these findings is emphasized by a significant age dependent increase of the risk for cardiovascular events in HIV-infected subjects.

Since the implication of new antiretroviral drugs at the end of the nineties, morbidity and mortality in HIV-infected patients have markedly decreased (Detels et al. 1998, Detels et al. 2001, Palella et al. 1998, Periard et al. 1999). In addition, the rate of opportunistic infections significantly declined in HIV-infected patients, accompanied with an improved CD4-rate. However, concerns of further HIV-associated manifestations rose. In particular, recent reports warned against the appearance of premature atherosclerosis in this patient population.

The reasons for premature atherosclerosis in HIV-infected patients are still unknown. A variety of authors speculated, that the side effects of new antiretroviral drugs, in particular effects on lipid- and glucose metabolism, may be responsible for an increased rate of cardiovascular events in this patient population (Fischer et al. 2001). However, different results were reported. While the study group for data collection on adverse events of anti-HIV drugs described a 26 percent relative increase in the rate of myocardial infarction per year by HAART (Lundgren et al. 2003), other large epidemiological studies analysing the mortality and hospitalisation rate for coronary heart disease and myocardial infarction in HIV-infected patients found no significant relation with the onset of HAART (Bozzette et al. 2002; Klein et al. 2002).

Nevertheless, HIV-infected patients present a significantly increase of premature atherosclerosis and an elevated rate of cardiovascular events, compared to HIV-negative people (Morgello et al. 2003; Klein et al. 2002). In previous studies we could demonstrate that HIV-infected subjects exhibit an increased cardiovascular risk profile, especially due to cardiovascular risk factors that were not influenced by HAART, such as gender, age and the rate of smoking (Neumann et al. 2003; Neumann et al. 2004). In addition, it had been assumed that the increased life span of HIV-infected patients may have a significant effect on the rate of cardiovascular events. However, at present, no specific age-related data concerning the cardiovascular risk factors and cardiovascular events in HIV-infected patients have been reported.

In the present study, we could demonstrate significant differences of cardiovascular risk factors and the probability of cardiovascular events in HIV-infected patients at different ages. Even if age has a tremendous effect by itself, further risk factors appear to intensify the risk of cardiovascular events. In particular, the alterations of lipid- and glucose metabolism primarily detected in older HIV-patients might have a significant effect on cardiovascular events. The reason for these metabolic alterations in older patients are unclear. However, it is interesting to recognise, that these changes are related to a continual increasing medication rate of protease inhibitors, emphasising the assumption on side effects of these drugs (Behrens et al. 1999; Carr et al. 1998; Periard et al. 1999; Walli et al. 1998). However, older HIV-infected patients also had an increased CDC-stage, possibly due to a longer time period of HIV-infection, and exhibited a different profile of HIV-acquisition.

No significant differences between younger and older patients were detected for cardiovascular risk factors not influenced by HAART, such as smoking rate and blood pressure. Nevertheless, the steady increase of total consumed tobacco, demonstrated by the package-years index, points to a relevant effect of this cardiovascular risk factor in older subjects, especially in combination with the elevated smoking rate seen in this population.

Thus, the risk of cardiovascular events in HIV-infected patients is significantly related to their age. Therefore, an increased duration of life due to a more effective antiretroviral therapy will have a significant impact on the rate of cardiovascular events in this patient population. In the future, further increase of cardiovascular events in HIV-infected patients may be expected.

REFERENCES

1. Assmann G, Schulte H, von Eckardstein A (1996) Hypertriglyceridemia and elevated lipoprotein (a) are risk factors for major coronary events in middle-aged men. Am J Cardiol 77: 1179-1184
2. Behrens G, Dejam A, Schmidt H, Balks HJ, Brabant G, Korner T, Stoll M, Schmidt RE (1999) Impaired glucose tolerance and beta cell function and lipid metabolism in HIV patients under treatment with protease inhibitors. AIDS 13:F63-F70
3. Bozzette SA, Ake CF, Tam HK, Chang SW, Louis TA (2003) Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. N Engl J Med 34: 702-710
4. Carr A, Samaras K, Burton S, Law M, Freund J, Chisholm DJ, Cooper DA (1998) A syndrome of peripheral lipodystrophy, hyperlipidaemia, and insulin resistance in patients receiving HIV protease inhibitors. AIDS 12: F51-F58.
5. Detels R, Munoz A, McFarlane G, Kingsley LA, Margolick JB, Giorgi J, Schrader LK, Phair JP (1998) Effectiveness of potent antiretroviral therapy on time to AIDS and death in men with known HIV infection duration. Multicenter AIDS Cohort Study Investigators. JAMA 280: 1497-1503
6. Detels R, Tarwater P, Phair JP, Margolick J, Riddler SA, Minoz A (2001) Effectiveness of potent antiretroviral therapies on the incidence of opportunistic infections before and after AIDS diagnosis. AIDS 15 :347-355
7. Fisher SD, Lipshultz SE (2001) Cardiovascular abnormalities in HIV-infected individuals. In: Braunwald E (ed) Heart disease: a text book of cardiovascular medicine. WB Saunders, Philadelphia, pp 2211-2221
8. Klein D, Hurley L, Quesenberry CP Jr, Sidney S (2002) Do protease inhibitors increase the risk for coronary heart disease in patients with HIV-1 infection? J Acquir Immune Defic Syndr 15 : 471-477
9. Lundgren JD et al. (The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group)) (2003) Combination antiretroviral therapy and the risk of myocardial infarction. N Engl J Med 349:1993-2003.
10. Morgello S, Mahboob R, Yakoushina T, Khan S, Hague K (2002) Autopsy findings in a human immunodeficiency virus-infected population over 2 decades. Arch Pathol Lab Med 126: 182-190
11. Neumann T, Woiwod T, Neumann A, Miller M, Ross B, Volbracht L, Brockmeyer N, Gerken G, Erbel R (2003) Cardiovascular risk factors and probability for cardiovascular events in HIV-infected patients: Part I: Differences due to the acquisition of HIV-infection. Eur J Med Res 8(6): 229-235
12. Neumann T, Woiwod T, Neumann A, Miller M, von Birgelen C, Volbracht L, Brockmeyer N, Gerken G, Erbel R (2004) Cardiovascular risk factors and probability for cardiovascular events in HIV-infected patients: Part II: Gender differences. Eur J Med Res 9(2): 55-60
13. Palella FJ Jr. Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, Aschman DJ, Holmberg SD (1998) Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med 338: 853-60
14. Periard D, Telenti A, Sudre P, Cheseaux JJ, Halfon P, Reymond MJ, Marcovina SM, Glauser MP, Nicod P, Darioli R, Mooser V (Swiss Cohort Study) (1999) Atherogenic dyslipidaemia in HIV-infected individuals treated with proteinase inhibitors. Circulation 100: 700-705
15. Walli R, Herfort O, Michl GM, Demant T, Jager H, Dieterle C, Bogner JR, Landgraf R, Goebel FD (1998) Treatment with protease inhibitors associated with peripheral insulin resistance and impaired oral glucose tolerance in HIV-1 infected patients. AIDS 12: F167-F173
16. Wilson PWF, D`Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB (1998) Prediction of coronary heart disease using risk factor categories. Circulation 97: 1837-1847

Received: December 23, 2003 / Accepted: January 12, 2004

Address for correspondence:
Till Neumann, MD
Department of Cardiology
University of Duisburg-Essen, Medical School
Hufelandstr. 55
D-45122 Essen, Germany
Tel: ++49 (0)201 723 3243
Fax: ++49 (0)201 723 3792
E-mail: till.neumann@uni-essen.de