® Postepy Hig Med Dosw (online), 2011; 65: 770-783
e-ISSN 1732-2693

www.phmd.pl
Original Article

Received: 2011.09.06
Accepted: 2011.11.14
Published: 2011.11.25

Subclinical carotid atherosclerosis and cardiovascular risk factors in HIV-infected patients*

Subkliniczne zmiany miażdżycowe tętnic szyjnych i czynniki ryzyka sercowo-naczyniowego u pacjentów zakażonych HIV

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Summary

Background: HIV infected patients, especially those treated with antiretroviral (ARV) drugs, show an increased risk and incidence of cardiovascular disease.

Objectives: The aim of this study was to evaluate the progression of subclinical atherosclerosis in the carotid arteries, expressed as the value of carotid intima-media thickness (cIMT) and the amount of atherosclerotic plaques, and to analyze the correlation between cIMT and risk factors for cardiovascular diseases in a cohort of HIV infected patients.

Methods: The analysis included 72 HIV infected patients, mean age 39.4 years, and 27 healthy HIV negative individuals, matched for age and sex. The data collected included evaluation of the infection, ARV treatment, past cardiovascular events, assessment of traditional and nontraditional risk factors for cardiovascular diseases, cIMT measurements and amount of atherosclerotic plaques in the carotid arteries.

Results: HIV infected patients show more advanced subclinical atherosclerosis in the carotid arteries (cIMT and plaques incidence). The cardiovascular risk profile of the HIV infected patients is significantly different from HIV negative people. Among the HIV positive group lower body mass index (BMI) and higher waist/hip ratio (WHR) are observed. The concentration of all cholesterol fractions is lower, whereas the concentration of triglycerides is higher. Cigarette smoking is more common among HIV-infected individuals. A strong statistical correlation between cIMT and age, hypertension, non-high-density lipoprotein (non-HDL) cholesterol and ARV time were found. Total and LDL cholesterol, and lifetime smoking exposure also affect the cIMT. The relationship between cIMT and current HIV RNA may indicate the impact of the current infection status on the cIMT dynamics in this subpopulation.

Key words: **HIV infection • cardiovascular risk • atherosclerosis • carotid arteries • cholesterol • non-HDL cholesterol • triglycerides • hypertension**

* This publication is part of the project "Wrovasc – Integrated Cardiovascular Center", co-financed by the European Regional Development Fund, within the Innovative Economy Operational Program, 2007–2013.

Streszczenie

Wstęp: U osób zakażonych HIV, zwłaszcza leczonych antyretrowirusowo, obserwuje się zwiększone ryzyko i występowanie chorób sercowo-naczyniowych.

Cele pracy: Celem pracy jest ocena zaawansowania subklinicznych zmian miażdżycowych w tętnicach szyjnych wyrażonych wartością cIMT (carotid intima-media thickness) i liczbą blaszek miażdżycowych oraz analiza zależności cIMT od czynników ryzyka chorób sercowo-naczyniowych w kohorcie osób zakażonych HIV.

Materiał/Metody: Do analizy włączono 72 osób zakażonych HIV, w średnim wieku 39,4 lata i 27 osób zdrowych, niezakażonych HIV, odpowiednio dobranych pod względem płci i wieku. Zgromadzone dane obejmowały: ocenę stanu zakażenia, leczenie antyretrowirusowe, przebycie incydentów sercowo-naczyniowych, ocenę tradycyjnych i nietradycyjnych czynników ryzyka chorób sercowo-naczyniowych, pomiar cIMT i liczba blaszek miażdżycowych w tętnicach szyjnych.

Wyniki/Wnioski: Osoby zakażone HIV wykazują istotnie większe zaawansowanie subklinicznych zmian miażdżycowych w tętnicach szyjnych (cIMT i liczba blaszek). Profil ryzyka sercowo-naczyniowego osób zakażonych HIV znamiennie różni się od osób niezakażonych – stężenia wszystkich frakcji cholesterolu są niższe, a triglicerydów wyższe, odsetek palaczy wiekszy, BMI niższe, a WHR wyższe. Poza wiekiem, stężeniem cholesterolu całkowitego i LDL oraz intensywnością dotychczasowego palenia, silny wpływ na cIMT mają cholesterol nie-HDL, nadciśnienie tętnicze i czas leczenia ARV. Związek między cIMT i aktualnym HIV RNA może wskazywać na wpływ aktualnego stanu zakażenia na dynamizm cIMT w tej subpopulacji.

Słowa kluczowe: **zakażenie HIV • ryzyko sercowo-naczyniowe • miażdżyca • tętnice szyjne • cholesterol • cholesterol nie-HDL • triglicerydy • nadciśnienie tętnicze**

Full-text PDF: http://www.phmd.pl/fulltxt.php?ICID=967075

Word count: 5596
Tables: 11
Figures: –
References: 83

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Introduction

Due to the continuous development of antiretroviral therapy in recent years and the significantly prolonged survival time of HIV infected patients, in addition to many other diseases coexisting with HIV infection, there have been numerous reports on increased risk of cardiovascular disease (CVD) in this subpopulation. In order to organize the knowledge on the subject, international medical circles involved in the care of HIV infected patients publish the results of their clinical observations, retrospective and prospective studies, including large prospective research programs, which reveal that this group of patients exhibits an increased risk of CVD incidence and that the progression of atherosclerosis is faster than in uninfected people [20,39,40,64,73].

Considering the research results, there are no single CVD risk factors in the HIV infected subpopulation. Currently, we can rather discuss etiopathogenic areas gathering the risk factors and determining faster development of atherosclerosis. The first of these risk areas is the incidence of well-known typical and non-typical risk factors in HIV infected patients, the existence and development of which, resulting from prolonged survival time, can be observed as in the general population. A statistically higher incidence of some classical risk factors such as male gender and smoking, or of nonspecific factors – lifestyle, low physical activity and poor diet – is characteristic of the HIV infected subpopulation [13,19,20,38,57]. Another area may be a proatherogenic effect of the combined antiretroviral therapy (cART), which is currently thought to directly activate the endothelium functioning, as well as a well-known phenomenon of metabolic disorders, such as dyslipidemia or insulin resistance, that promote the development of atherosclerosis [4,5,14,17,29,45,50,51,52,54,55,65,68,80]. The last and, as it currently seems, the most important role in pathogenesis in augmented atherosclerosis is played by chronic HIV infection, which, featuring a wide range of interactions with the host system, proinflammatory action of adhesion molecules, cytokines and infected lymphocytes, monocytes and mainly macrophages infiltrating the vessel wall, is a damaging factor for the vascular endothelium [6,11,28,36,47,56,61,63,67,70,78,79,82].

Atherosclerosis in HIV infected patients is evaluated using non-invasive research techniques, such as intima-media thickness measurement in the carotid and/or femoral arteries, brachial artery flow-mediated dilatation test or the

coronary artery calcium score [12,49]. The most popular tool to assess the severity and dynamics of atherosclerosis is ultrasound carotid intima-media thickness measurement (cIMT). cIMT as an important predictive factor favorably correlates with the risk of myocardial infarction and stroke, even after excluding the impact of other CVD risk factors. Finally, it is taken as a soft endpoint in clinical trials [8,13,17,35,37,44,49].

Aim of the study

The aim of this study was to evaluate the progression of subclinical atherosclerosis in the carotid arteries, expressed as the cIMT value and the number of atherosclerotic plaques, and to analyze the correlation between cIMT and CVD risk factors in a cohort of HIV infected patients treated and not treated with antiretroviral therapy. Moreover, the impact of HIV infection, infection duration, basic parameters of virological and immunological status over the course of infection and impact of the overall antiretroviral treatment duration on the development of the subclinical atherosclerosis were evaluated.

Material and methods

The study lasted from March 2008 to May 2009 and included 72 HIV infected patients treated at the Clinic of Acquired Immune Disorders.

The study group comprised 48 men and 24 women, mean age 39.4±8.9 years, including 68 ART-treated and 4 non-ART-treated patients. The inclusion criteria were a diagnosed HIV infection and the patient's informed consent to participate in the study. The following exclusion criteria were adopted: currently diagnosed acute medical condition, currently diagnosed AIDS, serum creatinine concentration higher than 2 mg%, more than 5-fold increase in transaminase levels. HIV infected patients entered the study with a known clinical, immunological and virological status of the HIV infection as well as HBV and/or HCV co-infections.

The control group comprised 27 healthy individuals (18 men and 9 women, average age 39.3 years ±10.9), inhabitants of the same region as the study cohort, respectively matched for age and sex, in good general condition, without history of cardiovascular events, not meeting the laboratory exclusion criteria adopted in the project.

This paper presents the preliminary cross-sectional results of the study on atherosclerosis in 72 HIV infected patients. The study was conducted with the approval of the Bioethics Committee.

The characteristics of the immunological and virological status of the study group are presented in Table 1.

The study protocol included obtaining the informed patient consent, interview with questions about traditional and selected non-traditional CVD risk factors, pharmacotherapy including cART, and symptoms of CVD: cerebrovascular and cardiac events, and intermittent claudication. A standard physical examination with anthropometric measurements of height, waist and hip circumference was performed to calculate the body mass index (BMI) and waist/hip ratio (WHR). Blood pressure measurement was performed in accordance with generally accepted standards. The patients were examined from the angiological point of view. Lower limb ischemia was evaluated on the basis of claudication in the interview and angiological examination and the ankle-brachial index (ABI) using a continuous wave Doppler detector, assuming the value <0.9 as incorrect.

Table 1. Characteristics of the study group

Number of HIV infected patients	72	
Time since diagnosis of HIV – years (median)	8	
Number of patients treated with ARV	68	
Time of exposure to ARV – years (median)	5.5	
Number of patients not treated with ARV	4	
Current CD4 + lymphocytes		
Total number of patients	476.5	(50–357)
Treated n=68	495.0	(50–1146)
Untreated n=4	425.5	(231–1357)
Nadir CD4 + (median) 79.5 (1–413)		
Total number of patients	196	(1–413)
Treated	194	(1–413)
Untreated	248	(23–380)
HIV RNA at the time of the study (median)		
Below detection level n=61	<50 copies/ml	
Detectable n=11	2 279 copies/ml (56–334000)	
Virological failure n=4	7 756 copies/ml (2270–220000)	
Zenith n=44	106 000 copies/ml (88–1829345)	
AIDS history	21	(27.7%)
HCV infection	30	(41.6%)
HBV infection	12	(16.6%)
Transmission mode		
Heterosexual	23	(31.9%)
MSM/bisexual	22	(30.5%)
Intravenous drug use	27	(37.5%)
Cumulative ARV time in months (median)		
NRTI n=69	110	(4–346)
NNRTI n=36	43	(1–198)
PI n=57	77	(2–225)

Hypertension was diagnosed if the patient had a history of diagnosed and pharmacologically treated hypertension or based on two pressure measurement results equal to or above 140/90 (at least first degree according to WHO).

Metabolic syndrome (MS) was recognized based on the NCEP ATP III (National Cholesterol Education Program Adult Treatment Panel III) criteria revised in 2004 and the assessment of waist circumference, typical for American standards, and the IDF (International Diabetes Federation) 2005 definition, with the waist circumference assessment typical for Europe [74,76].

Ischemic heart disease was recognized on the basis of the medical history, and a resting electrocardiogram (ECG) was performed in all patients. Exercise ECG had been planned in the case of a medical history suggesting angina, but so far there have been no indications for the exercise test in any of our patients. In all patients, a duplex ultrasound of carotid and vertebral arteries was performed, their patency assessed and ultrasound images recorded for further processing in order to evaluate subclinical atherosclerosis by means of computer-measured cIMT. Carotid artery stenosis was recognized according to the NASCET (North American Symptomatic Carotid Endarterectomy Trial) and Bluth criteria. Carotid ultrasound was performed using a high-resolution ultrasound GE LOGIQ 7 GE with broadband linear probe 6–12 MHz and 5x magnification. Four series of images were collected for each patient: left common carotid artery (LCA), right common carotid artery (RCA), left bulb (LB) and right bulb (RB). The images were recorded in three projections for each series – anterior, lateral and posterior. Far wall images of the distal common carotid arteries and bulbs were recorded parallel to the probe surface at the smallest artery diameter and then saved on the hard drive and on DVDs. cIMT was measured using a specially designed computer program. For each projection of a given series, manual cIMT measurement within a 1 cm long section was performed and 10 measurement points were established (30 measurement points per series, 120 points per patient). Atherosclerotic plaque was assessed using a criterion treating the plaque as focal IMT growth >1.5 mm. The measurement results were transferred to a database analyzing a number of statistical features for the measurements of each projection and series. The main parameter for each patient was the average IMT value obtained for all the series, defined as cIMT. Ultrasound examinations and cIMT measurements were performed by the same angiologist, a doctor with eighteen years of experience in vascular ultrasound and cIMT measurements [41,42,43]. Intra- and interobserver reproducibility tests of the cIMT measurement in the common carotid arteries and bulbs were carried out using the Bland and Altman plot and the intraclass correlation coefficient (ICC). The assumptions of the Bland and Altman plot were met, and the correlation coefficients for the intra- and interobserver reproducibility tests were 0.99.

Laboratory tests

The serum HIV RNA level was determined using the Roche Amplicor 1.0 standard assay (detection threshold 40 copies/mL), and CD4 T cells were counted by means of FACScan flow cytometry (Becton-Dickinson).

After 14 hours of fasting, blood samples were collected for other laboratory tests carried out by standard methods: complete blood count, transaminase level, creatinine, glucose, total cholesterol, HDL cholesterol, triglycerides, lipoproteins (a), homocysteine, fibrinogen, D-dimers, wrCRP (wide range C-reactive protein – latex-enhanced immunoturbidimetry) levels. LDL cholesterol was calculated according to the Friedewald equation, and non-HDL cholesterol by subtracting HDL from TC (total cholesterol). The presence of anti-HIV, anti-HBc and anti-HCV antibodies was determined in the control group using the enzyme immunoassay (EIA) method with microparticles.

Statistical analysis

Quantitative variables were presented as an arithmetic mean, geometric mean or median, depending on normality of distribution. For each estimator, 95% confidence intervals were calculated. Qualitative variables are presented as the number of patients in each group. Differences in quantitative features between the study and control groups were analyzed by Student's t-test, the Welch test or the Mann-Whitney test, respectively. To achieve normality, the logarithmic transform was applied to the variable elements. Differences in the qualitative features were analyzed using the χ^2 test or Fisher's exact test (for small groups). The correlation between continuous variables was described using Pearson's or Spearman's correlation coefficient (depending on the normality of data). The effect of clinical features on the cIMT value in the studied group was assessed using univariate or multivariate regression. The multivariate analysis employed the stepwise method, which removed all statistically insignificant features from the model.

The analysis was made using R and MedCalc statistical packages. All results with a significance level $p<0.05$ were considered significant.

Due to the small number of ARV non-treated patients in the cohort, the differences between ARV treated and non-treated patients were not analyzed in this study. The effect of drug class on subclinical atherosclerosis was not considered either, as individual therapy might have changed several times before the beginning of this study.

Results

Tables 2 and 3 show the statistical analysis of quantitative variables in the studied cohort and the control group.

Among the laboratory parameters relevant to the CVD risk assessment (Tables 2, 3), statistically significant changes in the lipid profile can be observed: in the study cohort, the level of all cholesterol fractions was significantly reduced and triglyceride concentration was higher, while in the hemostatic system, a significantly lower platelet count and fibrinogen concentration was recorded. No differences were found in the average concentration of lipoprotein (a) between the two groups. Other tests revealed lower hematocrit in the infected group; this difference is at the border of statistical significance. Fasting glucose, CRP and the homocysteine level did not differ significantly between the two groups. Table 4 shows the prevalence of classical risk factors in the study and control group.

Table 2. Quantitative characteristics of the experimental and control groups – arithmetic and geometric mean, and confidence interval – Student's t-test

Studied variable	Study group		Control group		P
	Mean	95% CI	Mean	95% CI	
Age (years)	39.4	36.3–41.5	39.3	35.0–43.6	NS
BMI*	23.6	22.9–24.4	25.6	24.2–27.0	0.01
WHR	0.92	0.90–0.94	0.86	0.82–0.90	0.002
Waist (cm)*	85.1	82.6–87.8	84.0	79.7–88.5	NS
Hips (cm)*	93.0	91.3–94.8	98.3	95.7–101.0	0.002
RRs mmHg	128.9	124.4–133.4	123.0	116.3–129.7	NS
RRd mmHg	81.3	78.0–84.6	79.6	73.6–85.6	NS
TC (mg%)*	183.1	172.7–194.1	214.5	201.5–227.3	0.0003
LDL-C (mg%)	100.7	92.3–109.0	127.2	115.7–138.6	0.0007
HDL-C (mg%)*	52.8	48.8–57.2	61.2	54.9–68.3	0.046
Non-HDL (mg%) *	124.2	113.9–135.5	148.6	134.8–164.0	0.007
TG (mg%)*	141.1	124.3–160.1	103.6	80.9–132.5	0.017
Lp(a) (g/l) *	0.08	0.06–0.10	0.06	0.04–0.09	NS
CRP (mg/l)*	0.54	0.37–0.78	0.56	0.28–1.12	NS
D-dimers (ng/ml)*	245.0	217.6–276.0	222.6	174.9–283.2	NS
Fibrinogen (g/l)*	2.4	2.3–2.6	3.0	2.8–3.2	<0.0001
Ht (%)	39.2	38.1–40.3	41.3	39.3–43.2	0.0489

* geometric mean.

Table 3. Quantitative characteristics of the experimental and control groups – median and confidence interval – Mann-Whitney test

Studied variable	Study group		Control group		P
	Median	95% CI	Median	95% CI	
cIMT (mm)**	0.648	0.625–0.703	0.514	0.461–0.544	<0.0001
Lifetime smoking (Pack-years)**	18	10.5–23.0	12.3	1.5–34.6	NS
Glucose (mg/dl)**	93.5	90.1–95.6	93.1	88.0–97.0	NS
Homocysteine (umol/l)**	13.10	11.50–13.55	12.20	10.21–13.11	NS
WBC (K/uL)**	5.5	5.05–6.01	5.85	5.17–6.38	NS
PLT (K/uL)**	215.0	200.3–238.0	261.0	242.9–329.2	<0.001

** data with non-normal distribution – median and 95% CI.

Among the major risk factors, tobacco smoking is the most representative and covers 2/3 of the cohort. Such parameters as current and past smoking, considered as categorical variables, differentiate the two groups to a statistically significant degree.

Another risk factor is hyperlipoproteinemia, understood as hypercholesterolemia, hypertriglyceridemia or mixed disorders. The proportion of these changes is similar in both groups (Table 4), but there are significant qualitative differences (Table 5). In the study group, dominant disorders involve dyslipidemia or hypertriglyceridemia, and in the control group, the dyslipidemia and hypercholesterolemia incidence is the same. No isolated triglyceride-related disorders were observed in the control group.

The percentage of diagnosed hypertension was similar in the cohort and in the control group (Table 4). Diabetes was found in two patients from the cohort and one person from the control group. A family history of CVD, assessed according to current guidelines, was positive in 29% of the infected patients and 14.8% of the control group. The differences are not statistically significant. The general assessment of body posture revealed a significantly higher waist-hip ratio (WHR) and a significantly lower body mass index (BMI) in the cohort participants

Table 4. Risk factors and metabolic profile in the test and control group, χ^2 test or Fisher's exact test

	Study group n=72		Control group n=27		P
CVD risk factors					
Age (mean)	39.39±8.94		39.26±10.85		NS
Male	48	(66.6%)	18	(66.6%)	NS
Hypertension	25	(34.2%)	9	(33.3%)	NS
Smoking					
Currently	46	(63.8%)	10	(37.0%)	0.04
In the past	13	(18.1%)	0	(0.0%)	0.04
Hyperlipoproteinemia	41	(56.9%)	14	(55.5%)	NS
Diabetes	2	(2.7%)	1	(3.7%)	NS
Positive family history of CVD	21	(29.2%)	4	(14.8%)	NS
Obesity (BMI >30)	6	(8.3%)	5	(18.5%)	NS
Metabolic syndrome ATPIII	19	(26.3%)	2	(7.4%)	0.05
Metabolic syndrome IDF	19	(26.3%)	2	(7.4%)	0.05

Table 5. Type of lipid disorders in the cohort and control group – χ^2 test or Fisher's exact test

Type of lipid disorder	Study group n=41		Control group n=14		P
Hypercholesterolemia	8	(11.1%)	7	(25.9%)	0.014
Hypertriglyceridemia	11	(15.3%)	0	(0.0%)	0.024
Dyslipidemia / mixed disorders	22	(30.6%)	7	(25.9%)	NS

Table 6. Comparison of IMT in the study group (n=72) and the control group (n=27) in different locations

Group	IMT LCA		IMT LB		IMT RCA		IMT RB		cIMT	
	GB	GK	GB	GK	GB	GK	GB	GK	GB	GK
Mean	0.612	0.474	0.761	0.564	0.600	0.501	0.839	0.655	0.703	0.549
SD	0.141	0.119	0.274	0.168	0.130	0.142	0.323	0.544	0.184	0.203
Median	0.586	0.428	0.675	0.554	0.581	0.457	0.716	0.530	0.649	0.507

LCA – left carotid artery, LB – left carotid bulb, RCA – right carotid artery, RB – right carotid bulb.

compared with the control group. WHR is markedly affected not by waist circumference, which is similar in both groups, but by hip circumference, and this is significantly lower among HIV infected people. Adopting two different definitions of the metabolic syndrome (MS) generated the same percentage of infected patients suffering from it, despite the fact that using different criteria resulted in obtaining two groups of the same size but of different composition. The MS incidence is higher than in the control group; the difference is on the border of statistical significance (Table 4).

Based on the physical examination, medical history and available medical records, cardiovascular disease was diagnosed in three of the cohort participants (4.2%). These three patients are exposed to multiple risk factors, including family history and hyperlipoproteinemia. Peripheral occlusive arterial disease with symptomatic lower limb ischemia (claudication) and reduced ABI value concomitant with coexistent asymptomatic high-grade stenosis of the carotid artery was found in one patient. Ischemic heart disease and a previous stroke were discovered in one patient and ischemic heart disease alone in one patient. Thus, ischemic heart disease in the form of documented stable angina pectoris occurred in 2.8% of the respondents, ischemic stroke in 1.4% and peripheral occlusive arterial disease (POAD) in 1.4% of the study cohort. Asymptomatic high-grade carotid artery stenosis (80%) was identified in one infected patient, and in another one, stenosis was slight (< 50%). One healthy man from the control group showed features of slight carotid artery stenosis.

Table 6 presents the results of IMT measurements: mean, standard deviation, median, minimum and maximum IMT for the location (LCA, LB, RCA, RB) and cIMT in both groups – the cohort and the control group.

Table 7. Characteristics of atherosclerotic lesions in the carotid arteries in the HIV infected group and the control group

Changes in carotid arteries	Study group N=72	Control group N=27	P
Stenosis/stenosis degree	1 patient / 80% 1 patient / 40%	1 person / 40%	
cIMT (mm)	0.703±0.184 (0.458–1.292)	0.549±0.203 (0.359–1.370)	<0.0001
IMT RB (mm)	0.839±0.323	0.655±0.544	<0.0001
IMT LB (mm)	0.761±0.274	0.564±0.168	<0.0001
IMT LCA (mm)	0.612±0.141	0.474±0.119	<0.0001
IMT RCA (mm)	0.600±0.130	0.501±0.142	<0.0002
Atherosclerotic plaque	25 (34.7%)	2 (7.4%)	0.005

Table 8. Univariate and multivariate regression – cIMT and risk factors in the study group

Risk factors	Univariate regression		Multivariate regression R2=0.59	
	Regression Coefficient	P	Regression Coefficient	P
Age	0.01375	<0.0001	0.01086	<0.0001
Gender	0.02977	NS		
Smoking	–0.05161	NS		
Hypertension	0.1461	0.003	0.1146	0.017
TC	0.001287	0.004		
LDL-C	0.001798	0.004		
HDL-C	–0.0003229	NS		
Non-HDL	0.001324	0.0028	0.0009626	0.01
TG	0.0002949	NS		
Lp(a)	–0.128	NS		
BMI	0.007768	NS		
WHR	0.4491	0.088		
ARV duration	0.01169	0.003	0.00601	0.048
Duration of HIV infection	0.006063	0.074		
Family history of CVD	–0.00139	NS		

In the group of HIV infected patients, the values of cIMT and IMT for each location (RB, LB, LCA and RCA) were significantly higher, as was the percentage of people in whom atherosclerotic plaques were found (Table 7).

Analysis of the effect of CVD risk factors and duration of HIV infection and ARV treatment time on the cIMT value (Table 8) carried out using univariate regression indicates the relationship between cIMT and the age of HIV infected patients, hypertension, total cholesterol concentration, LDL cholesterol, non-HDL cholesterol and duration of the ARV treatment. The final model obtained after multivariate regression analysis employing the stepwise method shows that the cIMT value strongly correlates with age, hypertension, non-HDL cholesterol concentration and duration of ARV treatment.

Analysis of regression between cIMT and smoking as a categorical variable shows no correlation of smoking and cIMT (Table 8). However, the correlation between a quantitative parameter (“pack-years”) and cIMT indicates a close positive relationship of cIMT values and lifetime smoking exposure, and cIMT is significantly higher in HIV-positive smokers compared with non-infected smokers (Table 9). There is no difference in cIMT between smokers and non-smokers in the cohort. At present, these validations are not strong enough due to the low number of smokers in the control group and non-smokers in the cohort.

Table 9. Lifetime smoking (pack-years) – statistical analysis of the effect of smoking on cIMT among cohort smokers and control smokers

Effect of smoking on cIMT in the HIV infected cohort – Spearman correlation			
Smokers (ever) HIV-positive	Corr. coeff.	95% CI	P
59	0.420	0.184–0.610	<0.001
Difference in cIMT between cohort smokers and non-smokers – Student's t-test for logarithmic data			
HIV-positive	Smokers (ever)	Non-smokers	P
N	59	13	NS
Mean	0.691	0.648	
95% CI	0.647–0.737	0.583–0.719	
cIMT difference between smokers from the cohort and the control group – Mann-Whitney test			
	HIV-positive smokers	HIV-negative smokers	P
N	59	10	0.009
Median	0.665	0.422	
95% CI	0.627–0.718	0.435–0.748	

Table 10. cIMT and selected virological and immunological quantitative characteristics of the cohort – Spearman correlation

Variable	n	Corr. coeff.	95% CI	P
Current CD4 T lymphocytes	72	0.068	–0.167–0.295	NS
Nadir CD4 T lymphocytes	70	–0.139	–0.037–0.089	NS
Nadir-time CD4 T lymphocytes	70	0.229	–0.006–0.441	0.056
Current HIV RNA	72	0.293	0.066–0.492	0.012
Zenith HIV RNA	43	–0.052	–0.347–0.252	NS
HIV RNA zenith - time	43	0.231	–0.075–0.497	NS

Correlation analysis (Table 10) of the infection and immunological status quantitative parameters indicates a weak correlation between cIMT and the current HIV RNA value (p=0.012).

After dividing the cohort according to the assumed criterion of treatment duration, a significant difference in the advancement of subclinical carotid atherosclerosis was revealed. Patients treated with ARV therapy for over 5 years have a higher value of cIMT.

MSM mode infected patients show a significantly higher cIMT value compared with a subgroup of those infected by intravenous drug use. No present correlation between cIMT and co-infection with HBV, HCV or AIDS history was observed (Table 11).

Further analyses of the study cohort showed a significantly higher cIMT value in infected patients with diagnosed hyperlipoproteinemia compared to the subgroup with a normal lipid profile. No significant effect of MS on the cIMT value was proven.

Discussion

The paper on the cohort of HIV infected patients evaluating the cardiovascular risk and subclinical atherosclerosis brought about a number of interesting observations. Atherogenic lipoprotein concentration is lower than in healthy subjects, duration and intensity of smoking (lifetime smoking) are similar among the infected and healthy people, blood rheological properties appear to be more favorable than in the control group, but still the severity of subclinical atherosclerosis in the carotid arteries expressed as the cIMT value and the amount of atherosclerotic plaques is significantly higher among infected patients compared to the age and sex adjusted control group. The statistical analysis reveals a more complex relationship between cIMT and CVD risk factors and certain characteristics of the infection and ARV treatment.

In the study group of HIV-positive patients, the rate of cardiovascular events is higher for men and lower for women (0%) compared to the general population. In the general English population, this percentage for men aged 16

Table 11. Analysis of cIMT dependence on selected clinical features of the study cohort

Feature	Current or with increased risk potential	Absent or with low risk potential	P
Gender Geometric mean 95% CI	Men n=48 0.691 0.644–0.743	Women n=24 0.666 0.604–0.733	NS
ARV treatment duration Geometric mean 95% CI	>5 years n=36 0.743 0.682–0.808	≤5 years n=32 0.624 0.583–0.669	0.002
AIDS history Median 95% CI	AIDS (+) n=21 0.642 0.560–0.677	AIDS (–) n=51 0.680 0.627–0.754	NS
HBV infection Geometric mean 95% CI	HBV (+) n=12 0.635 0.56–0.71	HBV (–) n=60 0.691 0.647–0.738	NS
HCV infection Arithmetic mean 95% CI	HCV (+) n=30 0.686 0.620-0.752	HCV (–) n=42 0.714 0.652-0.775	NS
Hyperlipoproteinemia Geometric mean 95% CI	(+) n=41 0.724 0.669–0.783	(–) n=31 0.632 0.586–0.682	0.017
Metabolic syndromeATP III Geometric mean 95% CI	MS (+) n=19 0.738 0.651-0.836	MS (–) n=53 0.664 0.623-0.706	0.097
Metabolic syndrome IDF Geometric mean 95% CI	MS (+) n=19 0.717 0.646-0.795	MS (–) n=53 0.665 0.621-0.712	NS
Transmission mode*			
(1) HTX (+) n=23 0.72 (2) IDU (+) n=27 0.645 (3) MSM (+) n=22 0.780			Different ($p<0.05$) from factor (3) (2)

* ANOVA test, Student-Neuman-Keuls test for all pairwise comparisons.

to 64 is 2% and for women 0.9% [27]. In the Spanish population, it is 4.3% [3].

The frequency of symptomatic POAD, confirmed by ABI, is similar (1.3%) to the non-infected population of this age [3] and twice as low as in the other described HIV infected cohorts [23,60].

It is difficult to discuss the impact of HIV infection on the incidence of CVD in our cohort in a clear way given the sample size and the number of people with episodes (one of the CVD events happened before HIV infection was documented), and also taking into account the exposure to multiple risk factors, including such potent factors as age, gender and positive family history.

The results of numerous studies, and mostly of the SMART study [64], which confirmed a higher rate of cardiovascular diseases among patients who interrupted cART compared to those treated in a continuous manner, indicate the impact of HIV infection on changes in the cardiovascular system. There are reports suggesting that cART may be an additional risk factor for the development of cardiovascular disease [20,29,50].

The prevailing classic risk factor in our cohort is smoking, followed by lipid disorders and hypertension. The prevalence of risk factors in the adult Polish population is different. The strongest risk factors are lipid disorders and then hypertension followed by smoking.

Comparison of this young cohort with the results of epidemiological studies in Poland is not easy, as all major studies were conducted among the elderly population. An analysis of incidence and intensity of risk factors was performed for a separate group aged 18-59 in the NATPOL PLUS study, and this will often be referred to in the discussion. Comparison of individual risk factors with the Polish epidemiological data shows an overrepresentation of smokers in the cohort, 63.8% of patients, while the percentage of smokers in the adult (18–59) Polish population is about 38%, which is the same as in the matched age and sex

control group (37%) in this study [83]. This traditional risk factor is emphasized in many papers on HIV infected patients. Usually, the percentage of smokers is similar to that shown in our study, while in the Warsaw HIV cohort, it is very high at 90% [9,18,30,34,35,37,51,61,70]. Quantitative evaluation by means of lifetime smoking suggests a relationship between cIMT and smoking intensity over time: the more intense and longer the smoking period, the further the progress of subclinical atherosclerosis, which was also reported by Hsue [30]. Two surprising facts are lack of difference in cIMT between smoking and non-smoking HIV infected patients, and a significant cIMT difference between infected and non-infected smokers. The probable explanation for both cases, apart from the small number of infected non-smokers and non-infected smokers, may be the complex character of the infection, ARV treatment and the accompanying metabolic disorders that reduce the differences among infected patients and exacerbate the differences between infected and non-infected participants.

The second most important risk factors in our cohort are lipid disorders, which occur in a similar proportion in the cohort and the control group (53% *vs.* 51%) and are convergent with NATPOL PLUS epidemiological data for the Polish adult population (50%) [83]. However, the Polish population is dominated by hypercholesterolemia (approximately 55–60%) [62,77,83]. Comparison of lipid disorders in these two groups demonstrated substantial qualitative differences. In the study group, significantly lower total cholesterol and LDL and HDL cholesterol levels were observed, and hypercholesterolemia was three times less frequent than in the control group (8.3% *vs.* 25.9%). Dyslipidemia or isolated hypertriglyceridemia prevail in the infected group, and the average triglyceride level in the cohort is statistically higher than in the control group and compared with Polish epidemiological studies, where the average concentration of triglycerides in a comparable age group is lower [83]. The total percentage of infected patients with a high triglyceride level is 43%. Similar data can be found in many papers on lipid disorders in HIV infected people. Usually, the induction of these disorders is linked to antiretroviral treatment, as the disorders may be affected by all classes of drugs: protease inhibitors (PIs), nucleoside (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) [14,20,24,25,26,58,65].

The cause of low total cholesterol and both its fractions in HIV infected patients is not clear; possible explanations include the young age of the cohort, low BMI, improper diet and lifestyle, and coexisting hepatitis B and C, as well as cigarette smoking (effect on HDL). The mean total cholesterol concentration in infected patients is significantly lower than in the control group and lower than in Polish population studies for this age group [83]. Although the literature on this emphasizes the existence of such a configuration in the past, before the cART era, there are still similar results in some works on infected patients published within the last decade [13,24,25,26,47].

The proportion of hypertensive patients was similar in the cohort and control group; the results are comparable to the total adult population in Poland, where it is estimated at 29% to 74%, but in the age group 18–59 the figure is 19.1% [72,83]. And thus, in both our groups, the incidence of hypertension was higher than in the epidemiological studies of Poles of the same age. The occurrence of hypertension among HIV infected people, especially those receiving cART and with diagnosed lipodystrophy syndrome, has been described by other authors [18,24,31,68]. The prevalence of hypertension in individual cohorts varies – from a few percent up to 34% in the slightly older Italian cohort [21]. The D.A.D study (Data Collection on Adverse Events of Anti-HIV Drugs) indicates the impact of traditional CVD risk factors on blood pressure and lack of correlation between pressure and particular classes of antiretroviral drugs, with the exception of NNRTIs, which are correlated with a low risk of developing hypertension [75].

Diabetes occurs in the two groups at a similar frequency as in the adult Polish population aged 18–59 [83]. The mean fasting glucose shows no differences and is similar in both groups. In other cohorts, the incidence of diabetes seems to be higher. The percentage of diabetics among infected patients is 6–7.3%, depending on the authors [18,30,51].

A general assessment of body posture revealed significantly higher WHR and significantly lower BMI in the cohort participants compared with the control group. Obesity is almost twice less frequent than in the control group. A lower BMI in HIV-positive people was also observed by other authors [9,44]. In the adult population of Poles aged 18–59, in as many as 47.3%, the BMI was equal to or greater than 25, which is reflected in our control group. Considering only abnormal WHR as an expression of central obesity, abdominal obesity concerns 43.1% of our study cohort. In Poland, this percentage in the same age group is slightly higher at 45.4% (NATPOL PLUS). The predictive importance of WHR for CVD risk assessment in HIV infected people has not been established yet. Special attention should be paid when assessing central obesity using this index, especially in ARV treated patients, because its value may be higher due to the loss of fat around the hips and buttocks in the course of HIV-associated adipose redistribution syndrome (HARS) [46]. In the studies of Johnsen et al., both the waist and hip circumference affected WHR; however, the effect was stronger for the reduced hip circumference [37]. This situation was also confirmed in our cohort, in which high WHR is significantly affected by low hip circumference, and waist circumference is irrelevant and does not differentiate the two groups. This paper does not deal with the symptoms of lipodystrophy (which occurs in various forms in the majority of the cohort). This will be the subject of further studies.

Metabolic syndrome is significantly more frequently diagnosed in the cohort, using both ATP III and IDF criteria, and this is consistent with previous reports. The percentage of patients with MS was also similar to that found in other studies [7,21,35,54,81]. We were somewhat surprised by the identical percentage of people with MS diagnosed according to various criteria, taking into account low BMI in the cohort and no effect of waist circumference on the WHR. Usually, the percentage is higher after adoption of more flexible NCEP ATP III criteria. The relatively high percentage of MS according to IDF criteria was probably due to using a waist circumference consistent with European standards and strong representation of factors other than waist circumference. MS as a categorical variable shows no association with cIMT, which had already

been reported [37]. This observation is in contrast to other works showing the effect of MS on the cIMT value [2].

Observation of the basic hemostatic parameters is also interesting. Configuration changes may indicate chronic consumption of platelets and fibrinogen in an ongoing inflammatory process. Fibrinogen is an acute phase protein involved in the clotting process in response to infection. It is one of the major plasma proteins affecting the viscometric properties of blood. It may seem that its level in HIV infected patients should be higher than in healthy people, but the literature on this topic contains contrary reports. Some authors confirm higher concentrations of fibrinogen in a HIV infected cohort [26,30]. Low fibrinogen concentrations in HIV-positive individuals were also reported in other papers [1,26]. Fibrinogen concentration may differ depending on the type of antiretroviral drugs, as high concentrations were observed while using PI, and low concentrations were observed for drugs from the NNRTI group [48]. At the moment, we do not know what the reason for reduced fibrinogen levels in the cohort is and how important its observation is. Is this a symptom of deep pathology in the chain of inflammatory processes or a symptom of liver dysfunction? Possible causes may include malnutrition (as indicated by a significantly lower BMI) or the coexistence of other infections – hepatitis B or C – which may lead to the weakening of fibrinogen synthesis. D-dimers are higher in the cohort, but this difference is not significant compared to the control group. Results for the basic hemostatic parameters plus significantly lower hematocrit in the infected group may indirectly indicate that blood rheological properties should be more favorable than in the healthy group. The significantly lower mean platelet count in the infected group is easily explained by coinfections with HBV and HCV as well as thrombocytopenia, which often accompany the infection and the main pathogenic mechanisms of which are already known [69].

There is no difference in the homocysteine concentration between the infected and control groups. Elevated concentrations were observed by other authors, especially in HIV infected patients treated with cART [10]. An effect of homocysteine on cIMT progression in HIV positive people has also been reported [13].

CRP is an acute phase protein and a known marker of inflammation. Its elevated concentration is a risk factor for cardiovascular diseases. Despite the observations of other authors claiming increased concentration of CRP in HIV infected patients [30,59], our study showed no differences in CRP concentration between the infected and non-infected group. The mean CRP level is even slightly lower in the cohort. Noursadeghi M et al. believe that the higher CRP concentration in the HIV subpopulations may be associated with an inflammatory response in the course of HIV infection *per se* [59]. In our study cohort, approximately 40% of patients suffer from coexisting HCV infection, which may lead to lowering CRP levels, as indicated by the observations of other authors [66].

Our study in the cohort of HIV infected patients compared with an appropriately matched group of healthy subjects showed, similarly to other studies, significantly greater severity of subclinical atherosclerosis in the carotid arteries, assessed by cIMT measurements and the amount of atherosclerotic plaques [22,30,49,61,70]. The cIMT is higher in HIV infected subjects in all locations, both within the common carotid arteries and in the bulbs. The incidence of atherosclerotic plaques in our cohort is significantly higher than in the control group. These results are similar to those obtained by other researchers [31,35].

Multivariate regression analysis revealed that cIMT is strongly affected by age, hypertension, non-HDL cholesterol and ARV treatment time. Non-HDL cholesterol represents the most atherogenic cholesterol fractions (LDL and remnants). Although the concentration of non-HDL cholesterol in the study group is significantly lower than in the control group (as for other cholesterol fractions), this parameter seems to be a strong non-traditional risk factor for subclinical atherosclerosis among HIV infected patients. Badiou et al. showed a relationship of cIMT with non-HDL cholesterol in HIV individuals, using the univariate regression analysis [2]. A non-HDL cholesterol effect on cIMT progression has also been reported [14]. Both the cited works and our study indicate the need to use this parameter in assessing cardiovascular risk and as a secondary therapeutic target in connection with LDL cholesterol, as recommended by NCEP ATP III. Our observation is also practical: many HIV infected patients treated with ARV suffer from hypertriglyceridemia with triglyceride concentration exceeding 400 mg%, making it impossible to calculate LDL cholesterol. Given our strong observations, we believe that the assessment of lipid disorders in HIV infected patients should include the non-HDL cholesterol parameter, which is easy to calculate in a doctor's office. Total cholesterol and LDL cholesterol treated as individual risk factors also affect cIMT, despite a lower average level among HIV infected patients. The effect of these cholesterol fractions on cIMT progression was reported by others [14,31]. The relationship between cIMT and hypertension is most often evaluated based on quantitative data – the value of systolic or diastolic blood pressure. The use of a categorical variable allowed us to exclude the impact of incidental blood pressure fluctuations and demonstrate the connection of subclinical atherosclerosis development with long-term hypertension.

Present studies on the interrelation of cIMT and virological and immunological parameters show a weak positive correlation between cIMT and the current HIV RNA concentration. At this stage, we treat this result as an interesting tendency, which will be given more attention in further studies. The literature on this subject contains reports on testing the impact of HIV RNA on endothelial function using flow-mediated vasodilatation (FMD) in ARV non-treated patients [61]; yet no correlation was found between HIV RNA and cIMT. It is believed that cIMT growth is a long-term process, but dynamic changes within cIMT are now widely discussed. Our observation, if confirmed in further studies, may indicate dynamic changes of IMT in this relatively young subpopulation – the possibility of progression but also regression, which is suggested in the Coll study, where both phenomena were reported [9]. This possibility was confirmed in autopsy studies of people in the general population, who died at different ages, which showed that in young people the carotid arteries were dominated

by foam cell infiltrates, considered to be a reversible atherosclerotic formation [15]. The dynamic nature of the changes is also confirmed by the results of drug-based studies that demonstrated the regression of subclinical atherosclerosis expressed by IMT [53,71]. With this in mind, it can be assumed (and treated as a hypothesis) that the adverse period of HIV infection, confirmed by high viral load or a low number of CD4 T-cells, may result in an increased cIMT value. No effect of the number of CD4 T-cells on the cIMT value was found. Our observations are in line with studies that show the relationship of subclinical atherosclerosis with HIV infection *per se* [47,61,78]. Even in patients treated successfully with antiretroviral therapy, chronic immune activation continues, although at a low level [32]. It is known that persistent stimulation of the immune system, characteristic of HIV infection, accelerates the development of atherosclerosis. An atherogenic effect is observed both in the course of the immune deficit, as well as immune system stimulation related to antiretroviral treatment [28,31,32].

A history of AIDS, co-existing HBV and/or HCV infection did not significantly differentiate the cIMT value. Time of ARV treatment longer than 5 years is associated with greater severity of subclinical atherosclerosis in our cohort.

Conclusions

The cohort of HIV infected patients shows significant progression of subclinical atherosclerosis in the carotid arteries expressed by cIMT and incidence of atherosclerotic plaques. The atherosclerosis is strongly influenced by a complex set of risk factors such as age, non-HDL cholesterol, hypertension and duration of antiretroviral treatment. The cIMT is also affected by total and LDL cholesterol. Lifetime smoking exposure exerts a significant effect on cIMT. Based on the observation of a relationship between cIMT and current HIV RNA, we can claim an impact of the current infection status on the cIMT dynamics in this young subpopulation. Time of treatment longer than 5 years, as well as diagnosed hyperlipoproteinemia, are associated with significantly greater severity of subclinical atherosclerosis. The cardiovascular risk profile of HIV infected patients is significantly different from healthy people: the concentration of all cholesterol fractions and BMI are lower, whereas the concentration of triglycerides, percentage of smokers and WHR are higher. Higher WHR is dependent on hip circumference.

Metabolic syndrome occurs slightly more often in infected patients, but we did not demonstrate its effect on subclinical atherosclerosis. Important changes in basic hemostatic parameters were observed, and their causes and significance will be investigated in further studies.

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The authors have no potential conflicts of interest to declare.