

The prevalence of cardiovascular risks in HIV-infected persons in care in Croatia in 2015

Desbordes, Ivan Raymond Marius

Master's thesis / Diplomski rad

2016

Degree Grantor / Ustanova koja je dodijelila akademski / stručni stupanj: **University of Zagreb, School of Medicine / Sveučilište u Zagrebu, Medicinski fakultet**

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:105:953269>

Rights / Prava: [In copyright](#)/[Zaštićeno autorskim pravom.](#)

Download date / Datum preuzimanja: **2024-07-11**



Repository / Repozitorij:

[Dr Med - University of Zagreb School of Medicine Digital Repository](#)



**UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE**

Ivan Desbordes

**THE PREVALENCE OF CARDIOVASCULAR
RISKS IN HIV-INFECTED PERSONS IN CARE IN
CROATIA IN 2015**

Graduate Thesis



Zagreb, 2016

This graduate thesis was made at the University of Zagreb, School of Medicine at the department of Infectious Diseases, division HIV/AIDS, University Hospital Zagreb, mentored by Professor Josip Begovac, M.D., PhD, and was submitted for evaluation in 2016.

List of abbreviations:

ACC/AHA–American College of Cardiology/American Heart Association

AIDS–Acquired immunodeficiency syndrome

ASCVD–Pooled Cohort Atherosclerotic CVD risk equations

CART–Combination antiretroviral therapy

CHD–Coronary heart disease

CVD–Cardiovascular disease

DAD–Data collection on adverse events of anti-HIV drugs

EACS–European Aids Clinical Society Guidelines

ESC/EAS–European Society of Cardiology/European Atherosclerosis Society

FRS–The Framingham risk score

ART–Antiretroviral therapy

HDL–high-density lipoprotein (cholesterol)

HIV–Human immunodeficiency virus

IMT–Intima-media thickness

InSTI– Integrase strand transfer inhibitors

LDL–Low-density lipoprotein (cholesterol)

NNRTI–Non nucleos(t)ide reverse transcriptase inhibitor

NRTI–Nucleos(t)ide reverse transcriptase inhibitor

PI–Protease inhibitor

SCORE–European Systematic Coronary Risk Evaluation Score

TC–Total cholesterol

TG–Triglycerides

VLDL–Very low-density lipoprotein cholesterol

UHID – University Hospital for Infectious Diseases

Contents:

1. Summary	1
2. Introduction	2
3. ART-associated lipids disorders	3
4. Prevalence of cardiovascular risk in HIV-infected patients	6
5. Management of “high-risk for CVD” HIV-infected patients	20
6. Acknowledgements	25
7. References	25
8. Biography	29

Summary:

Title: "THE PREVALENCE OF CARDIOVASCULAR RISKS IN HIV-INFECTED PERSONS IN CARE IN CROATIA IN 2015."

Author:

Ivan Desbordes

Abstract:

Aim: This review will aim at considering the prevalence of cardiovascular risks among the HIV-infected population undergoing ART therapy in Croatia: Cardiovascular diseases are now among the most common causes of mortality in people living with HIV. We will see for which reasons people living with HIV appear to have an elevated risk for cardiovascular diseases.

Method: A cross-sectional analysis of 310 consecutive HIV infected patients seen during a routine clinical visit aged 40 to 79 years was performed in Zagreb from June 2014 to March 2016. All the next cardiovascular risks factors were systematically assessed: age, gender, race, total cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, smoking, diabetes (blood glucose measurements), treated for high blood pressure (yes or no), past and current history of ART (particularly, duration of treatment including abacavir, indinavir and lopinavir (DAD)). Were also systematically collected CD4+ cell count, HIV viral load, family history of premature CVD, past medical history of CVD.

Results: Among the 310 persons included into the study, 42% were current smokers, 23% were hypertensive, 34% had Hypercholesterolemia (>6.2 mmol/L), 38% of patients were overweight, 12% were obese, 27% exhibited metabolic syndrome, 7.8% of patients had past cardiovascular event, 12.9% patients had a family history of premature cardiovascular event, 21% of patients were already treated for high blood pressure, 18.4% were already treated with lipid-lowering agents, 46% of the studied population had an abacavir-including antiretroviral regimen, 10% of patients had a detectable viral load, and 11.6% of patients had a low CD4+ cell count (<350 per mm³).

Conclusion : : Among the HIV-infected persons in care in Croatia in 2015, the prevalence of a compound collection of major cardiovascular risk factors is high.

Key words: ART dyslipidemia prevalence cardiovascular risk Croatia

INTRODUCTION

The introduction of highly active antiretroviral therapy (HAART) combinations for human immunodeficiency virus (HIV)-infected patients, which was for the first time able to effectively suppress the replication of HIV and dramatically reduce both mortality and morbidity, has resulted in a better and longer quality of life for HIV-patients [1]. These innovative combinations have dramatically changed their life's perspectives [2].

The different ART combinations, all composed of at least three different antiretroviral drugs, can manage to reduce viral load to undetectable levels [3]. ART combinations prevent viral replication by acting at different stages of the viral replication cycle [4]. They are classified in different therapeutic groups according to their action's mechanism: integrase strand transfer inhibitors (INSTIs) [5], entry inhibitors [CC chemokine receptor-5 antagonists][6], fusion inhibitors [7], protease inhibitors (PIs)[8], nonnucleoside reverse transcriptase inhibitors (NNRTIs)[9] and nucleoside reverse transcriptase inhibitors (NRTIs)[10]. Aside from the substantial benefits on viremia that result from the use of various ART combinations, laboratory and clinical experience has shown that ART can induce severe and considerable adverse effects on metabolic complications of lipid metabolism, characterized by signs of lipodystrophy, insulin resistance, central adiposity, dyslipidemia, increased risk of cardiovascular disease and even an increased risk of atherosclerosis [11-14]. Noteworthy, other individual factors may be involved in the metabolic and lipid alterations observed because not all of the patients exposed to the same ART regimens are similarly affected [15-17]. All of these changes in the aspects of lipid metabolism during HIV infection, specifically changes in high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), very low-density lipoprotein cholesterol (VLDL), triglycerides (TG), lipid peroxidation, and their relationship with atherosclerosis in HIV-infected patients, are a result of the critical role of cholesterol in the mechanism of HIV replication [13,14,18,19]. HIV decreases plasma HDL by impairing the cholesterol-dependent efflux transporter ATP-binding cassette protein A1 in human macrophages, which is a condition that has a high atherogenic risk [20,21].

ART-associated lipid disorders:

Cardiovascular risk associated to PIs regimens

The use of PI-based ART constitutes a strong option against HIV infection because it prevents both the maturation of viral particles and controls the infection of new cells by HIV. Unfortunately this virological efficiency often goes along with changes in lipid metabolism in HIV patients and dyslipidemias have been associated with this class of antiretroviral drugs [11,12,22,23]. PIs are associated with increased hepatic triglycerides-synthesis, VLDL, and to a lesser extent, total cholesterol (TC) [11-14]. It has also been observed that these drugs impair the hydrolysis of triglyceride-rich lipoproteins by lipase, which reduces the storage of free fatty acids and interferes with the normal postprandial metabolism of free fatty acids [22,24]. The PIs are analogous substrates of the aspartyl protease enzyme of HIV that are involved in the cleavage process of viral proteins and form smaller functional viral particles with infective capacity. After the cleavage process, the newly formed infectious viral particles are released from infected cells in a mature form [8,25,26]. Once the PIs bind to the active site of the protease enzyme, and this process of cleavage is blocked, there is interference in the enzyme activity and inhibition in the process of viral maturation and the formation of infectious viral particles [25,26]. The different mechanisms by which PIs promote these changes remain unknown. However, the main effect of PIs seems to be suppressing the breakdown of the nuclear form of sterol-regulatory element binding protein-1 in the liver and adipose tissue. This regulator is a key element in the proteolytic pathway responsible for regulating cellular and plasma levels of fat and cholesterol [27].

Of course, other classes of antiretroviral drugs are available, including those with excellent activity against viral replication without having any apparent effect on lipid metabolism [13,22,28]; but it is clear that the use and recommendation of PIs occurs in situations where other drugs have not achieved the targeted effect, either by nonadherence to treatment, viral resistance or lack of an immune response [29,30]. Moreover, once the therapy with PIs is initiated, a change to a more conservative therapy without their use is not recommended nor used in clinical practice [31,32].

Thus, a continuous search that considers the individual characteristics of each PI available as a current therapy is needed to achieve alternative ART regimens that can maintain a suppression of viremia with minor effects on the lipid metabolism of HIV patients [31,33].

Cardiovascular risk associated to NRTIs

Evaluation of the potential contribution of nucleos(t)ide reverse transcriptase inhibitors (NRTI) on the increased cardiovascular risk in HIV patients on ART within the D:A:D study revealed an increased risk for myocardial infarction in patients being treated with abacavir or exposed to this drug within the preceding 6 months was reported for the first time [34]. These findings were confirmed by several studies, but not all: A french study based on Hospital database short-term/recent exposure to abacavir was associated with an increased risk of myocardial infarction in the overall cohort [odds ratio (OR) 2.01; 95% confidence interval (CI), 1.11–3.64] but not in the subset of matched cases and controls who did not use cocaine or intravenous drugs (OR:1.27; CI: 0.64–2.49). This has raised the question as to how far cohort studies can adjust for all potential confounding factors which may contribute to cardiovascular risk and which may have been over-represented in the abacavir-treated patients.

With regard to other NRTIs no increased risk has been found. Table 1 summarizes the main classes of antiretroviral drugs, their effects on lipid and glucose metabolism, and the potential for contributing to the risk of CVD. Azidothymidine, a NRTI and component of first line ART, has been described to cause cardiac dysfunction induced by mitochondrial toxicity [35,36] in two reports on adults, where three larger studies could not confirm any association between exposure to azidothymidine and myocardial dysfunction [37-39]...

Cardiovascular risk associated to NNRTIs

If Protease inhibitors (PIs) are recognized as having the greatest impact in terms of metabolic complications, followed by nucleoside reverse transcriptase inhibitors, the non-nucleoside reverse transcriptase inhibitors (NNRTIs) have the least impact [40] and appear to be among the most neutral regarding metabolic changes (dyslipidemias and glucose regulation impairment). In particular, regimens based on the NNRTI nevirapine have been shown to achieve significant metabolic benefits and may help to improve dyslipidemias.

Drug Class	Generic name	Effects on lipids	Effects on glucose	Impact on coronary artery disease
Nucleos(t)ide Reverse Transcriptase Inhibitors: (NRTI)	Abacavir(ABC)	TC↑ LDL↑	No effect	Increased risk of MI (controversial)
	Azidothymidine	TC↑ LDL↑	Insulin resistance+	No association
	Didanosine(ddI)	Dyslipidemia++	Insulin resistance+	No association
	Emtricitabine(FTC)	Neutral	No effect	No association
	Lamivudine(3TC)	Neutral	No effect	No association
	Stavudine(d4T)	Dyslipidemia +	Insulin resistance+	No association
	Tenofovir(TDF)	TC↓ LDL↓	No effect	No association
Non-Nucleoside Reverse Transcriptase Inhibitors : (NNRTI)	Efavirenz(EFV)	TC↑ LDL↑	No effect	No association
	Etravirine(ETR)	Neutral	---	---
	Nevirapine(NVP)	HDL↑	---	No association
	Rilpivirine(RPV)	Neutral	---	---
Protease Inhibitors: (PI)	Ritonavir	Dyslipidaemia +++	Insulin resistance +++	Cumulative exposure increases risk for MI
	Amprrenavir+ Ritonavir	Dyslipidaemia ++	Insulin resistance +	Cumulative exposure increases risk for MI
	Fosamprenavir+Ritonavir	Dyslipidaemia ++	Insulin resistance +	Cumulative exposure increases risk for MI
	Atazanavir+ Ritonavir	Dyslipidaemia +	Insulin resistance +	No association
	Darunavir+ Ritonavir	Dyslipidaemia +	Insulin resistance +	---
Indinavir	Dyslipidaemia +	Insulin resistance +++	Controversial results	
Lopinavir+Ritonavir	Dyslipidaemia+++	Insulin resistance +++	Cumulative exposure increases risk for MI	
Nelfinavir	Dyslipidaemia +	Insulin resistance +	No association	
Saquinavir	Dyslipidaemia +	Insulin resistance +	No association	
Tipranavir+ Ritonavir	Dyslipidaemia +	Insulin resistance +	---	
Integrase strand transfer inhibitors: (INSTI)	Elvitegravir+ Cobicistat	Neutral	No effect	No association
	Raltegravir	Neutral	No effect	No association
	Dolutegravir	Neutral	No effect	No association
Entry inhibitors: (CC chemokine receptor 5 antagonists)	Maraviroc	Neutral	No effect	---
	Enfuvirtide	Neutral	No effect	---

Table1: Main Classes of antiretroviral drugs and their impact on lipid and glucose metabolism and coronary artery disease. Dyslipidemia is defined by increased TC, LDL, TG and decreased HDL. MI, myocardial infarction. [41]

Impact of diabetes on cardiovascular disease in human immunodeficiency virus

Among the developed countries, an increasing proportion of the population is or will have to deal with diabetes mellitus: This growing civilization's disease turns to be a major public health issue and CVD is the leading cause of morbidity and mortality among diabetic patients [42].

For HIV patients, age, BMI and sex remain the major risk factors for diabetes mellitus [43]. No studies have been able to link HIV infection itself (in ART-naive patients) with diabetes mellitus, suggesting no increased risk of diabetes mellitus by HIV infection [44]; but increased rates of insulin resistance have been observed in ART-naive HIV patients. The risk of diabetes in HIV is enhanced once patients start on ART [43–45]. We already mentioned adverse effects Protease inhibitors over lipids metabolism, but they also reversibly increase insulin resistance, the risk of diabetes and subsequently the risk for CVD through the inhibition of glucose translocation through GLUT4 [46].

The NRTIs azidothymidine and stavudine appear to have a direct effect on glucose metabolism through mitochondrial toxicity [47,48].

A French systematic hospital database nationwide review has shown that the increased long-term risk for heart failure in HIV-infected compared with HIV-negative patients was independently associated with HIV +/- diabetes at 12-month follow-up [49]. These results advocate for the crucial importance of glucose monitoring in patients on ART, especially in patients on PIs and older NRTIs.

The prevalence of cardiovascular risks in HIV-infected patients in care in Croatia in 2015

The specific data concerning Croatia are arising from a cross-sectional study performed at the university hospital for infectious diseases "Fran Mihaljevic" Zagreb by Doctors

Vanja Romih Pintar and Pr.Dr Josip Begovac. Due to the fact that Croatia has a centralized system of treatment and care of persons infected with HIV, the data collected there are therefore national.

Objective: This analysis aimed at assessing and specifying the prevalence of cardiovascular risk factors among the HIV-infected population at the UHID Zagreb.

Method: Over a period starting from June 2th 2014 to March 14th 2016, 310 consecutive HIV infected patients have been examined during a routine clinical follow-up visit. They were aged 40 to 79 years and were retracted from the study in case of acute illness or exacerbation of chronic illness at the time of the evaluation. Pregnant women were also excluded. All the next cardiovascular risk factors were systematically assessed: age, gender, race, total cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, smoking, diabetes (blood glucose measurements), treated for high blood pressure (yes or no), past and current history of ART (particularly, duration of treatment including abacavir, indinavir and lopinavir (DAD)). Were also collected CD4+ cell count, HIV viral load, family history of premature CVD, past medical history of CVD.

Relying on the data collected during this cross-sectional study, have been compared four cardiovascular disease risk models: The Framingham risk score (FRS), the Pooled Cohort Atherosclerotic CVD risk equations (ASCVD), the European Systematic Coronary Risk Evaluation Score (SCORE) and the Data Collection on Adverse Effects of Anti-HIV Drug study (DAD). Patients have been categorized according to these four CVD risk models in "high cardiovascular risk patients" and "non high cardiovascular risk patients". High risk: FRS-10y > 20%; SCORE-10y > 5%; ASCVD-10y > 7,5%; DAD -5y > 5%.

Definitions

CVD was considered present if a history of any of the following conditions existed on inclusion into the study: myocardial infarction, stable/unstable angina, invasive coronary artery procedure, carotid artery disease (symptomatic like transient ischemic attack or stroke, or >50 percent stenosis on angiography or ultrasound), stroke, peripheral artery disease, abdominal aortic aneurysm or other forms of clinical atherosclerotic disease (eg, renal artery disease).

Family history of premature cardiovascular events was considered present if the event occurred in a male first-degree relative <55 years or female first degree relative <65 years.

Diabetes mellitus was defined if at least two fasting plasma glucose levels were ≥ 7.0 mmol/L, casual plasma glucose > 11.1 mmol/L, or if patient had a history of diabetes treatment.

Arterial hypertension was defined as systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg ($> 135/85$ mm Hg in diabetic patients) or taking antihypertensive drugs.

Blood pressure was measured by the attending nurse using mercury sphygmomanometers. The patient was in a seated position; his or her arm was supported and flexed at the level of the heart. The stethoscope's bell was lightly pressed over the brachial artery just below the cuff's edge. The first knocking sound (Korotkoff) indicated the patient's systolic pressure and the disappearance of the knocking sound indicated diastolic pressure.

Dyslipidemia was considered present if total cholesterol > 6.2 mmol/L, HDL-cholesterol < 1.03 , or fasting triglycerides > 2.26 mmol/L. The modified updated National Cholesterol Education Program criteria were used for the definition of metabolic syndrome: triglycerides of at least 1.7 mmol/L, HDL of 1.0 mmol/L or less in men and of 1.3 mmol/L or less in women, hypertension (systolic blood pressure > 130 mm Hg or diastolic blood pressure > 85 mm Hg), or use of antihypertensive medications and a glucose level at least 5.6 mmol/L or the diagnosis of diabetes.

Body mass index was used as a surrogate for waist circumference.

Results: The global results indicate that the prevalence of major CVD risk factors is **high** in Croatia among the HIV-treated population in 2015. See details of independent risk factors below:

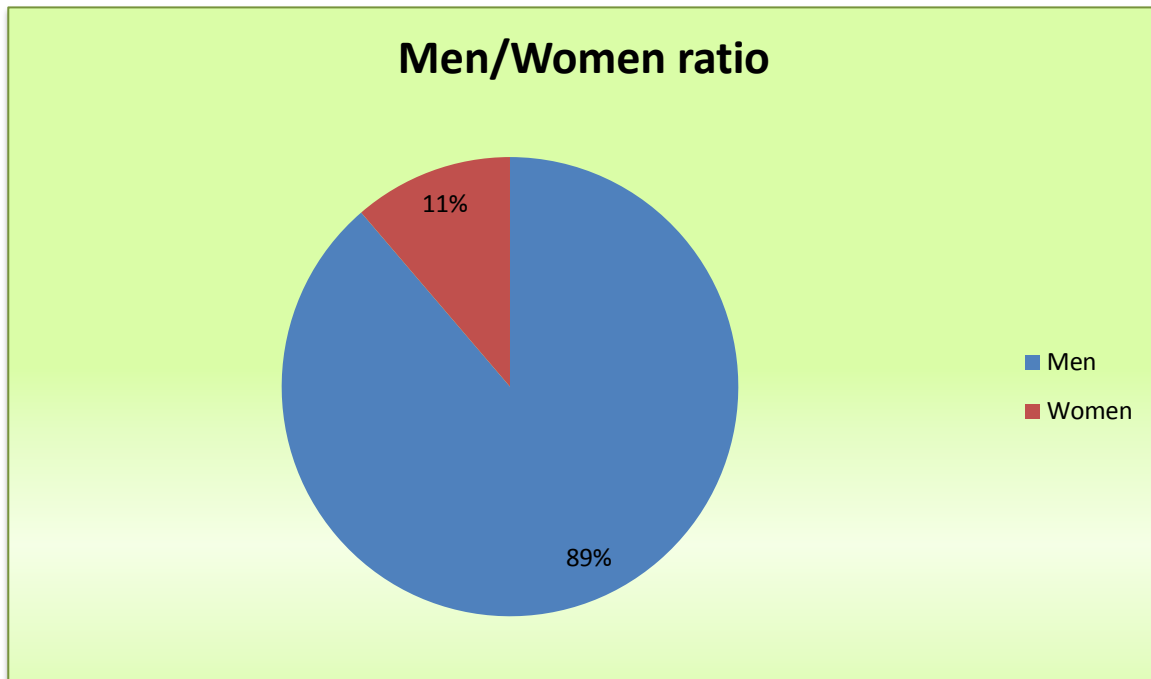


Figure1: Men/Woman ratio.

In the studied population, men are overrepresented compared to the general population, they are **89%**(figure 1). Male sex is a risk factor for cardiovascular diseases.

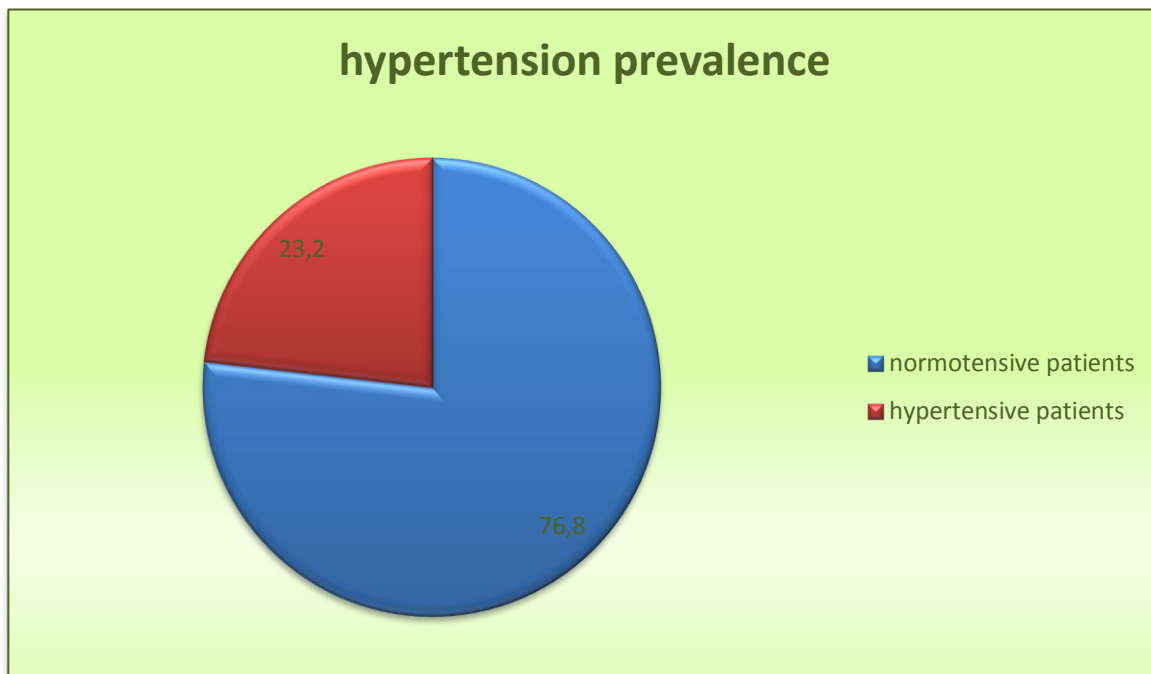


Figure 2: Hypertension prevalence.

Hypertension prevalence is significantly high in the studied population, it reaches **23.2%** (figure 2) According to European guidelines of the European Society of Cardiology and European

Atherosclerosis Society (ESC/EAS), hypertension is one if not the main leading independent risk of cardiovascular event (with age).

Individual ART regimens:

Figure 3: individual ART combination.

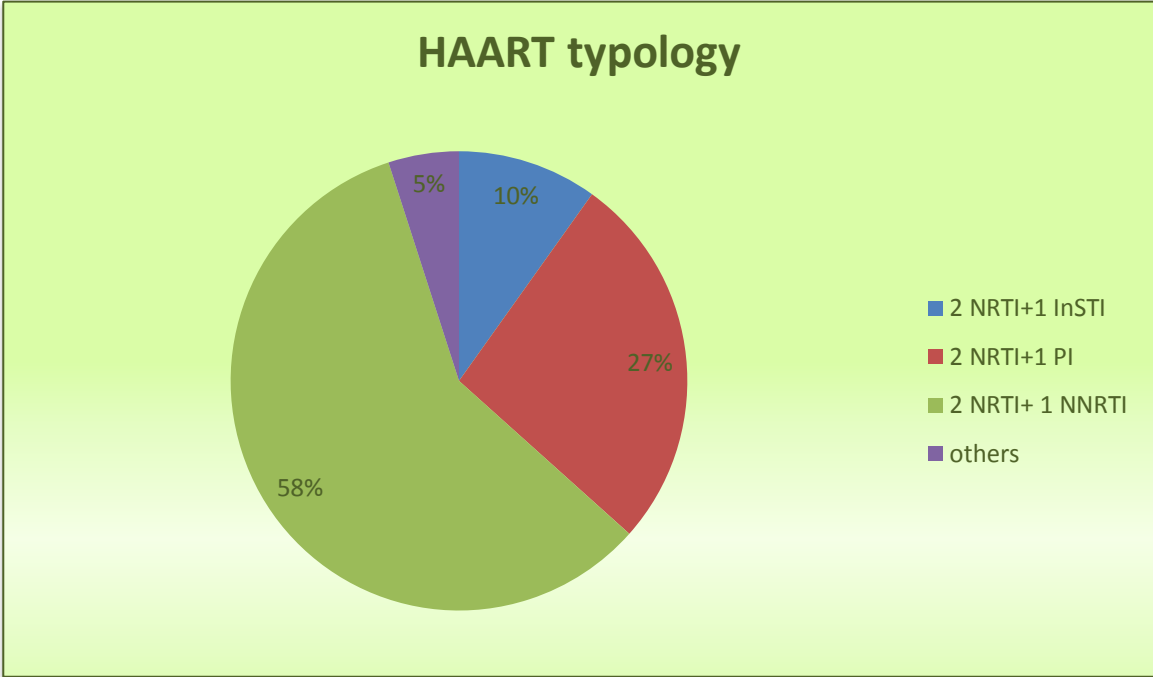
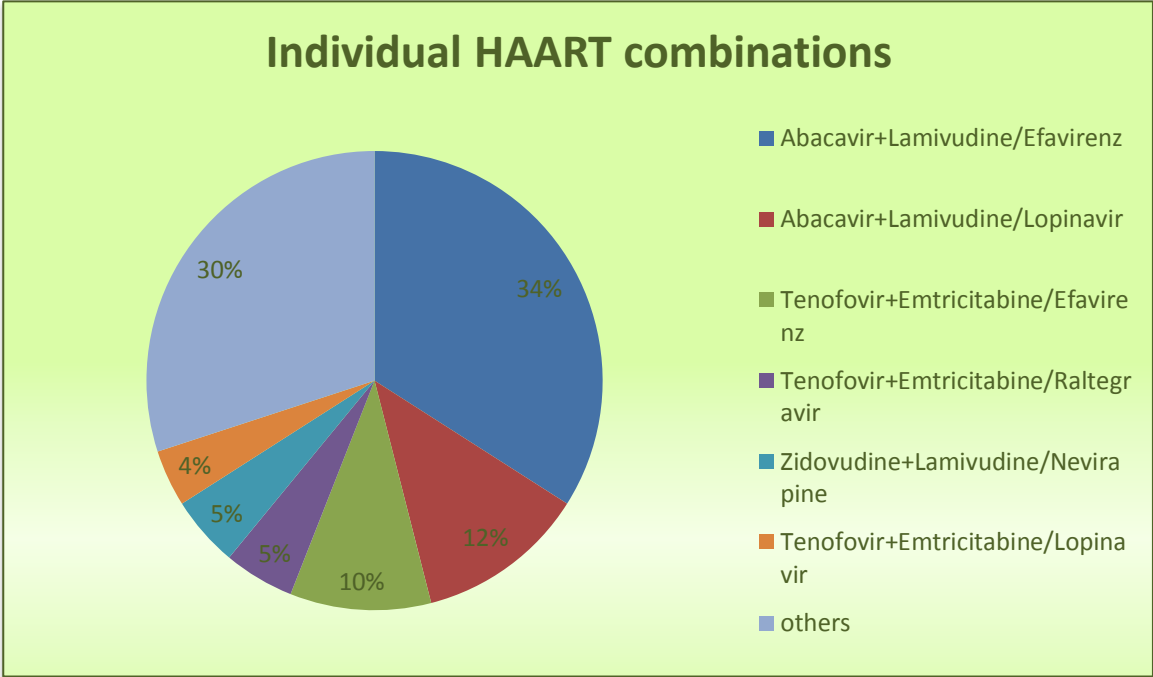


Figure 4: ART Types.

As previously stated, some combinations are more susceptible to induce dyslipideamias and its consequence, atherosclerosis, than others:

- **27%** of patients are having a PI-included ART combination (figure 4).
- Among the 58% of patients treated with 2 NRTI+1NNRTI, only 10% are treated with nevirapine, others are treated with efavirenz which is less favorable regarding the lipids metabolism (figure 3).

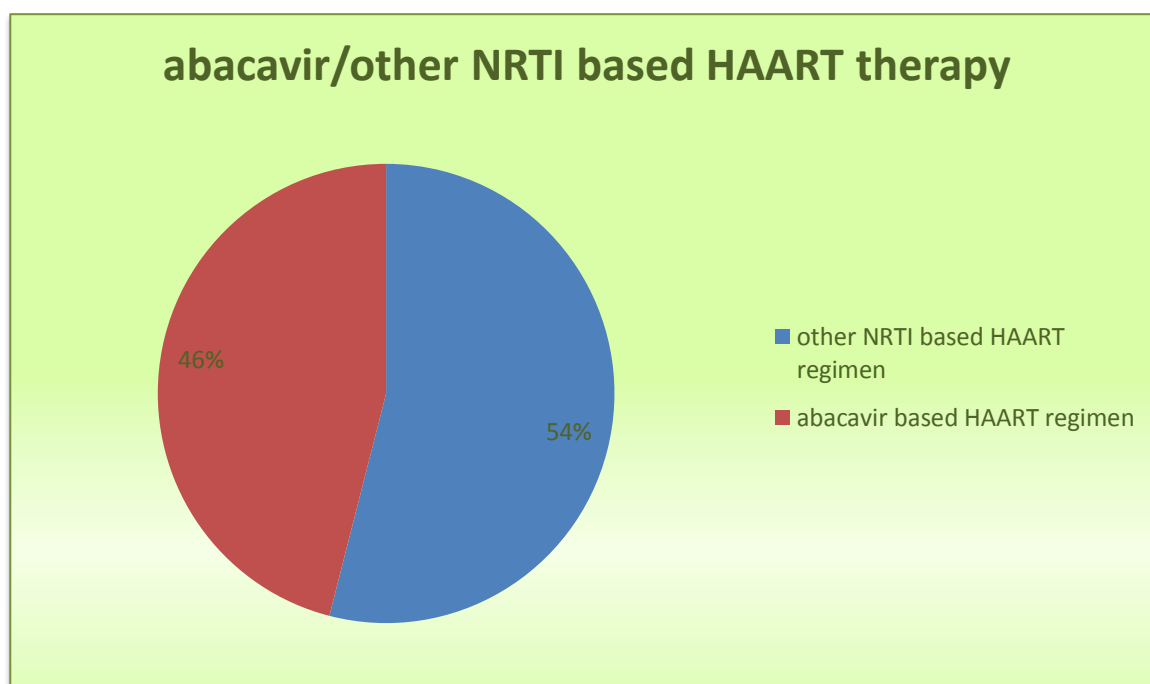


Figure 5: abacavir based-/non abacavir-based regimens.

Abacavir is suspected to be related to an elevated risk of myocardial infarctions[34].

- **46%** of the studied population have an abacavir-including regimen.(figure 5)

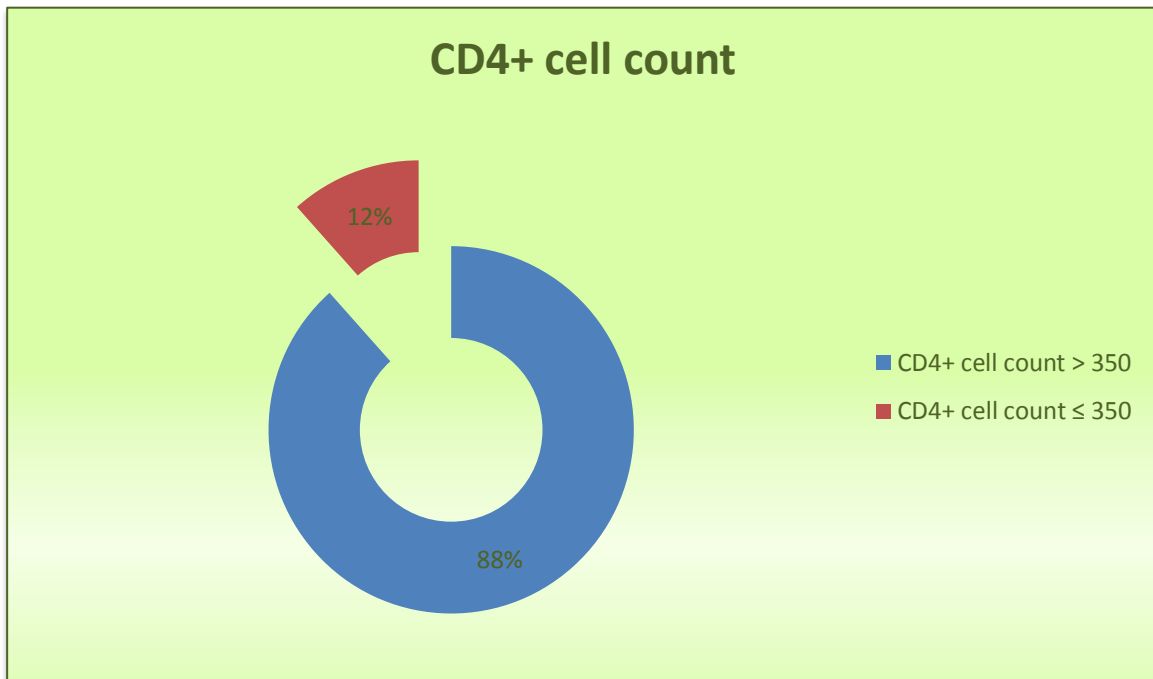


Figure 6: CD4+ cell count.

Low CD4+ T cell count is a risk factor for cardiovascular disease events [50]

In the studied population, **11.6%** of patients have a low CD4+ cell count (figure 6).

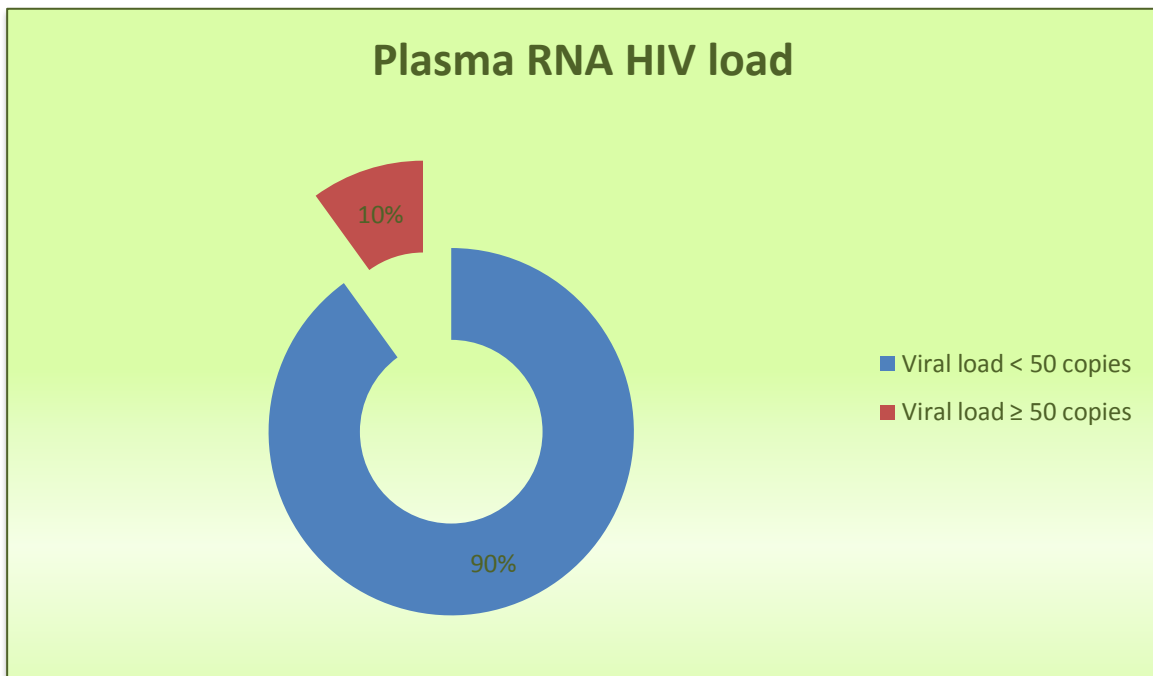


Figure 7: Viral load.

A statistically significant relationship exists between high HIV RNA load and low HDL-cholesterol [50,51]

- In the studied population, **10%** of patients have a detectable viral load (figure 7).

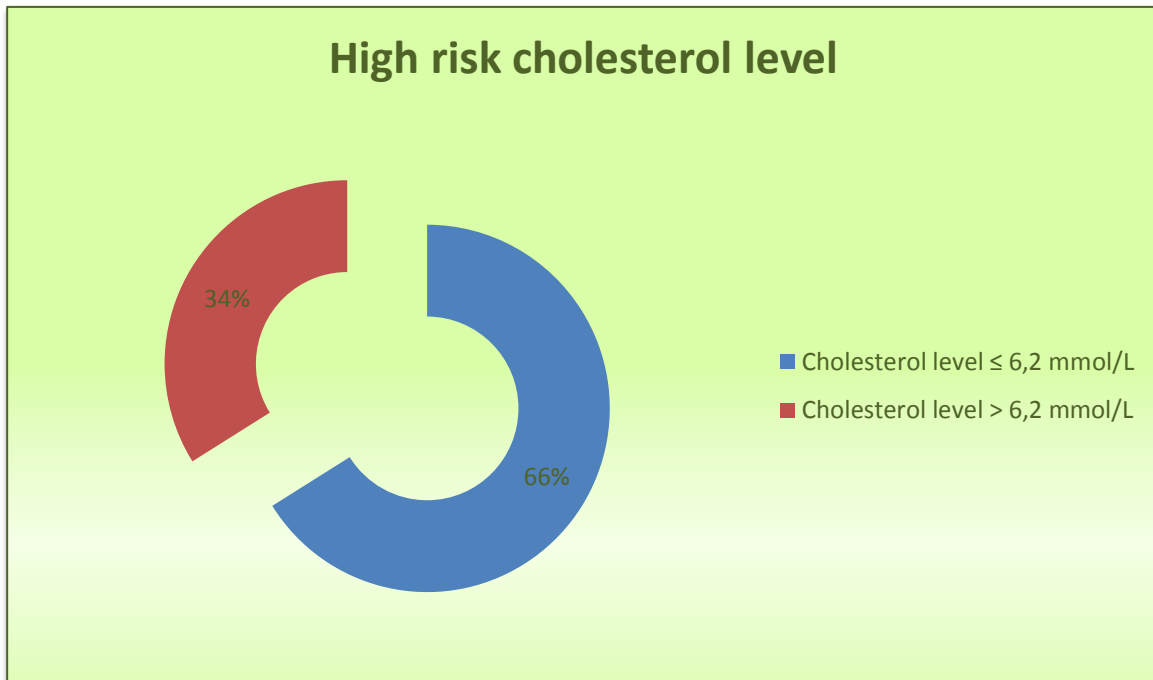


Figure 8: proportion of patients above/below the "high risk" threshold of 6.2mmol/L of cholesterol (TC)

Cholesterol level above 6.2mmol/L were found in 33.9% of individuals (figure 8).

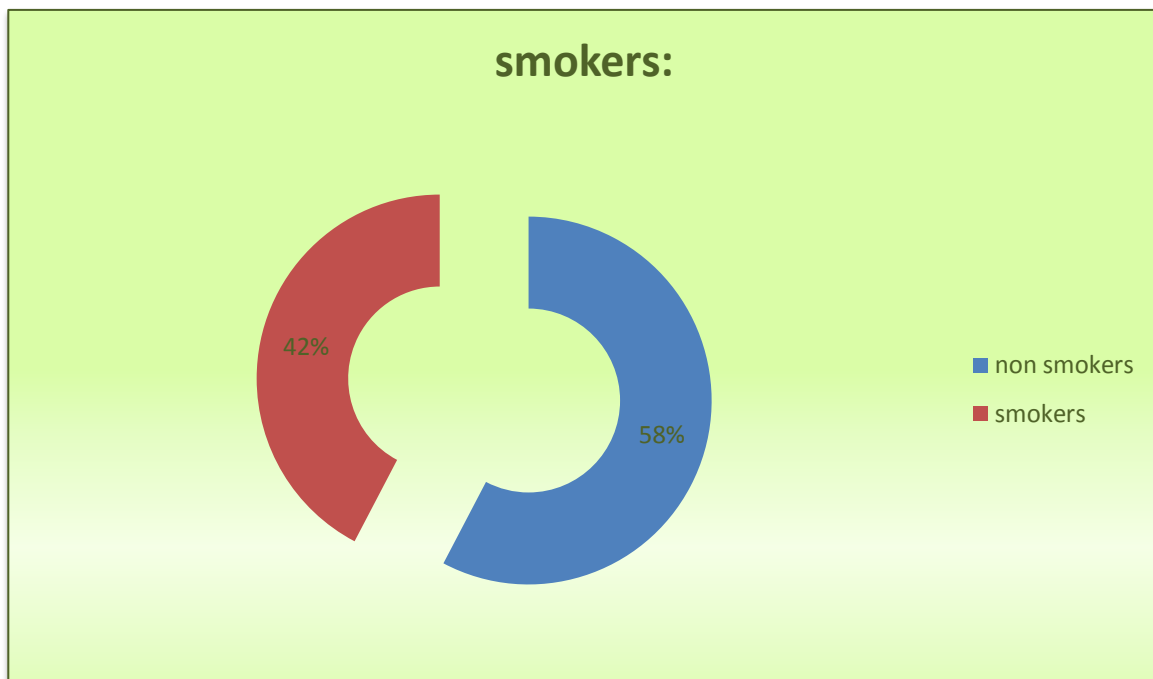


Figure 9: prevalence of smokers.

A very high prevalence of smokers (**42.3%**) is contained in the Croatian HIV treated population (figure 9). Not only this population smokes more than the general population, but its body mass index (BMI) repartition is worrisome:

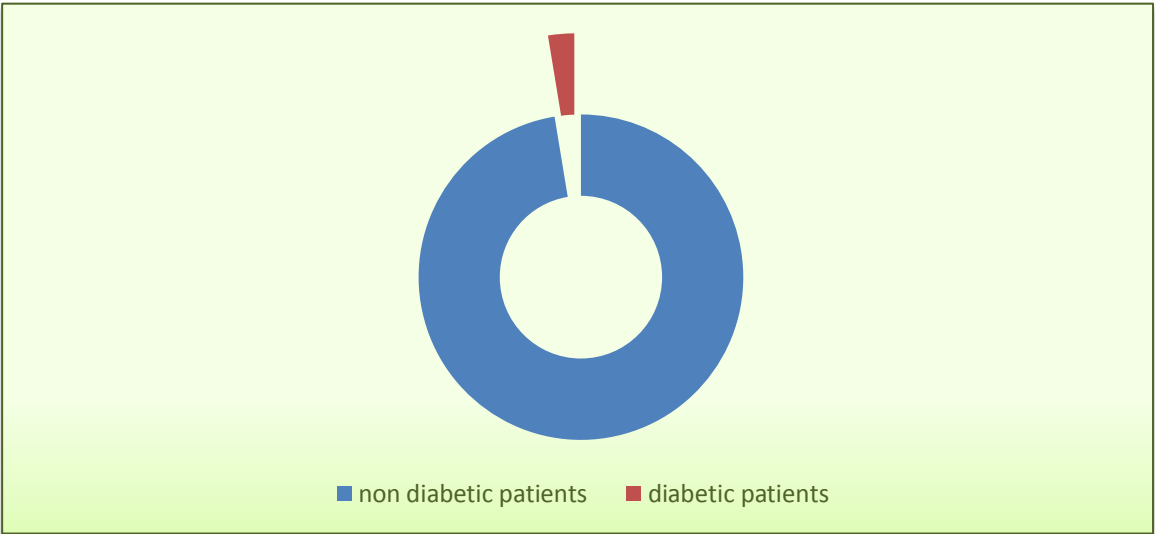


Figure 10: Prevalence of diabetes in HIV-infected population in care:

In the studied population, **2.6%** of patients exhibit diabetes (figure 10).

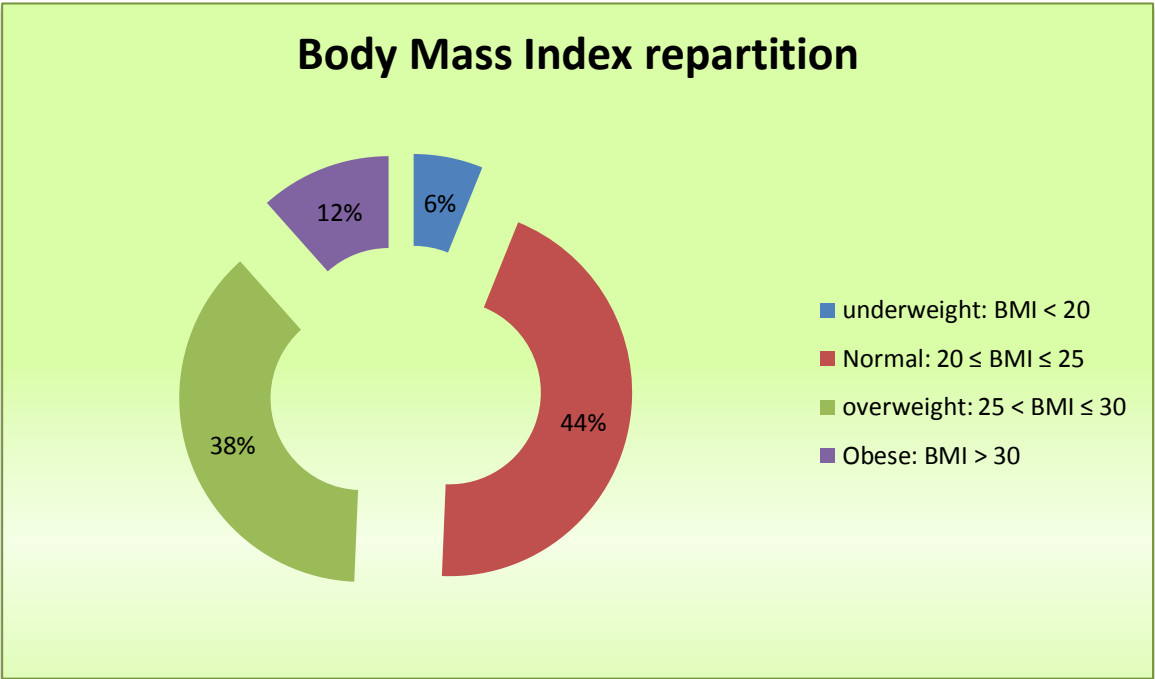


Figure 11: repartition of corpulence.

- In the studied population, **37.7%** of patients are overweight.
- And **11.6%** are obese (figure 11).

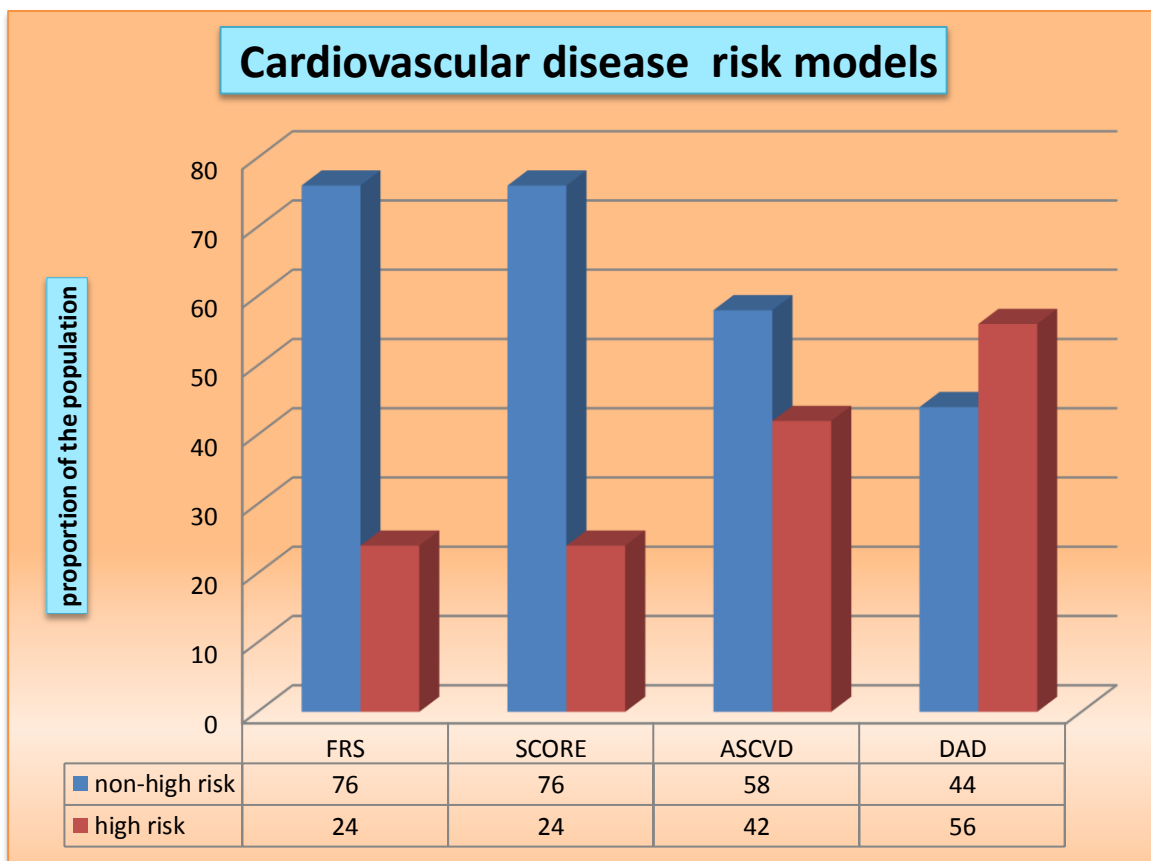


Figure 12: Studied population screened by 4 risk models. The proportion of high and non-high scores are reported.

Even though, the non HIV-specific models are not assessing the CVD risks with a similar range than the DAD does, the global conclusion remains that the prevalence of major CVD risk factors **is high** in Croatia among the HIV-treated (figure 12).

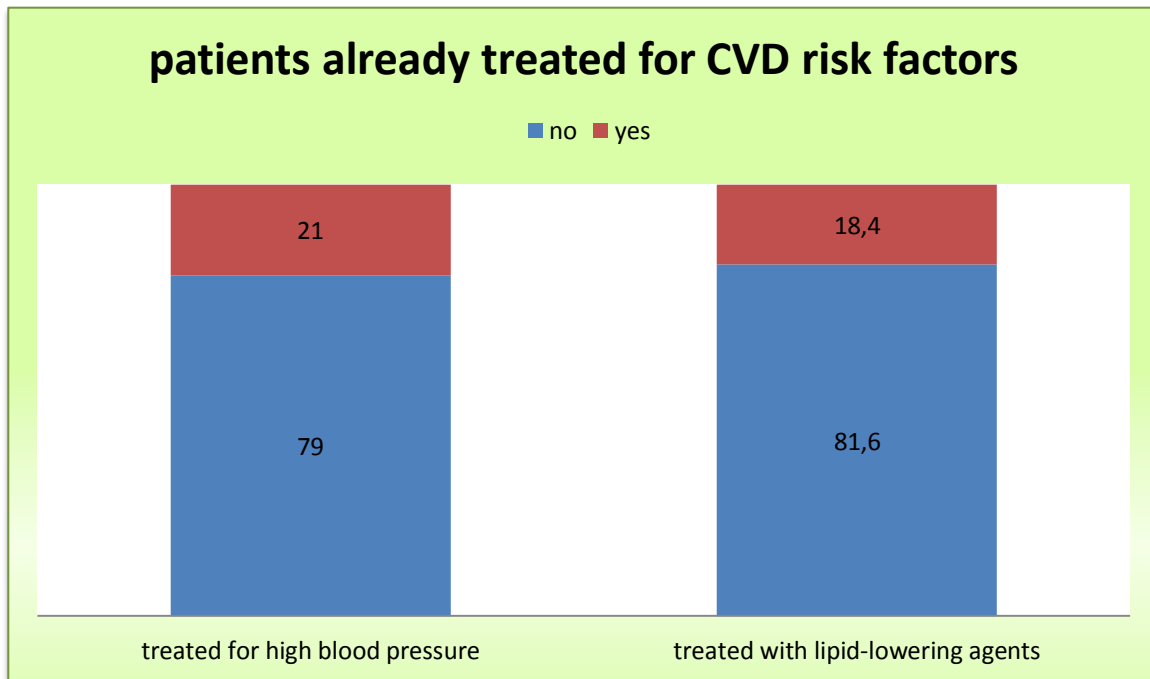


Figure 13:proportion of patients already undergoing treatment against CVD risk factors.

In the studied population, **21%** of patients are already treated for high blood pressure, and **18.4%** are already treated with lipid-lowering agents (figure 13).

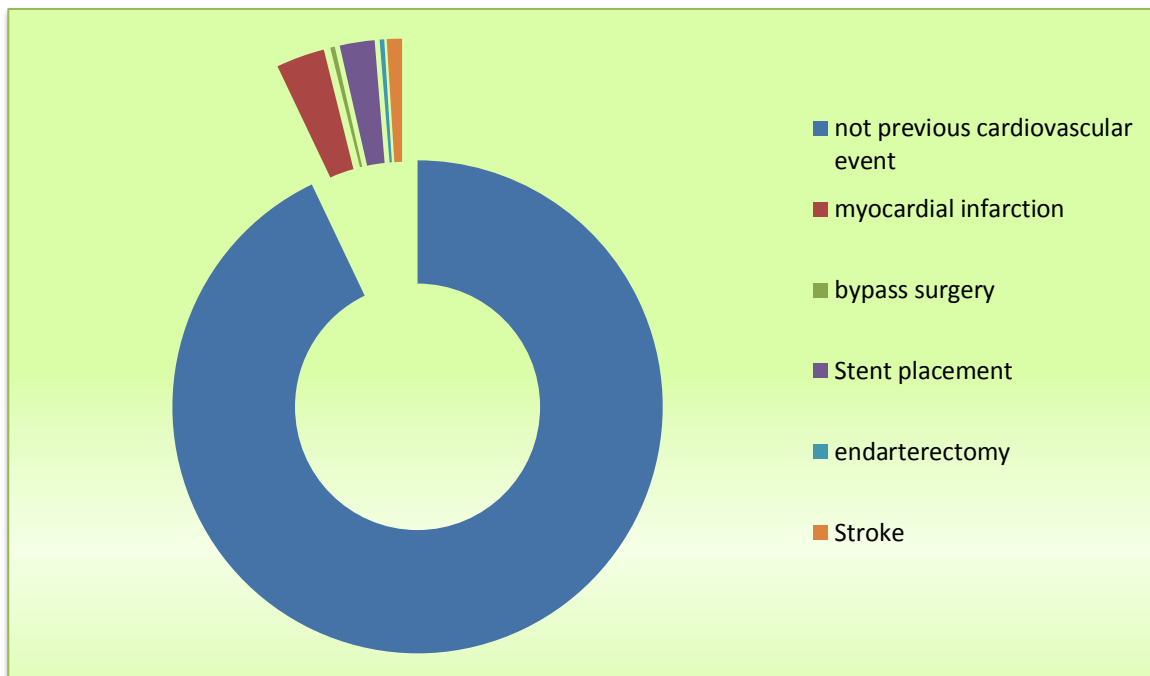


Figure 14: Proportion of patients with past cardiovascular event.

In the studied population, 3.2% of patients suffered previous myocardial infarction, 0.3% underwent bypass surgery, 2.3% stent placement, 1% endarterectomy and 1% suffered stroke. In total, 7.8% of patients had past cardiovascular event (figure 14).

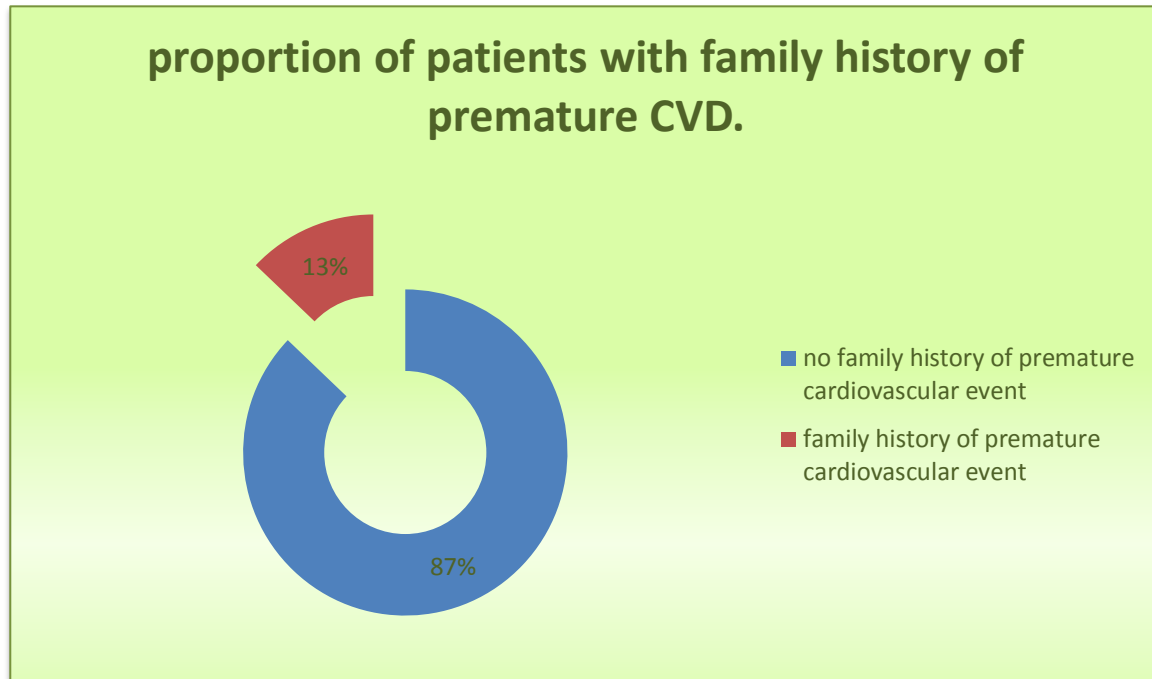


Figure 15: proportion of patients with family history of premature cardiovascular event.

In the studied population, 12.9% of patients have had a family history of premature cardiovascular event (figure 15).

Discussion

We found a high prevalence of different cardiovascular risk factors in HIV-infected persons in Croatia older than 40 years.

As previously stated, HIV-infected patients have metabolic abnormalities that make them susceptible to atherosclerosis. These abnormalities are caused by the combined effects of HIV infection itself, toxicities of specific antiretroviral therapies, as well as the traditional factors that increase atherosclerotic risk in the non-HIV-infected population: age, gender, smoking, overweight and obesity (Body mass index), systolic and diastolic blood pressure (hypertensive patients), previous cardiovascular event (the patient is then in secondary or tertiary prevention) total cholesterol, HDL-cholesterol and diabetes mellitus.

Assessing the exact level of influence of the HIV-infection as an independent factor and thus establishing equivalences with the non-infected population's risk models is challenging:

Some studies have considered the intima-media thickening of carotid arteries (higher specificity with internal carotid arteries) as an efficient marker of atherosclerotic evolution and thus as a CVD predicting factor. Comparing the intima-media thickening of the carotid arteries correlated with different factors could therefore measure the relative influence of the HIV infection as an independent risk factor compared to the other traditional CVD risk factors. Comparisons in between HIV population and controls (after adjustment for demographic and traditional CVD risk factors) have revealed that HIV-infection induced intima-media thickening was similar to the effects associated with male gender, smoking status and diabetes mellitus [51]. These findings suggest that HIV infection can be considered as an independent risk factor for atherosclerosis similar to the level of risk associated with male gender, smoking status and diabetes.

Among the HIV-infected population in care in Croatia in 2015, a high number of patients need interventions to reduce their cardiovascular disease risks. About one fifth to more than one third of patients, depending on the risk equation used, need intensive lifestyle modifications (cessation of smoking, diet, or weight loss) and lipid lowering therapy.

Certain drugs used for HIV treatment, like lopinavir/ritonavir, indinavir/ ritonavir, amprenavir, and fosamprenavir have been associated with an increased risk for myocardial infarction [table 1]. Abacavir has also for long been correlated (controversially) with CVD. Guidelines recommend its cautious use in patients with a high CVD risks. However, in Croatia abacavir is frequently used due to the higher cost of tenofovir- based formulations compared to abacavir formulations.

Another study, also based on the previous four prediction models, assessed the prevalence of eligibility for lipid lowering therapy among a HIV-infected population extended to Serbia (Belgrade and Zagreb combined HIV-treated population, forming a larger sample, very similar to the Croatian subgroup though) [53].

The statins eligibility was assessed according to the 2013 American college of cardiology/American heart association (ACC/AHA) guidelines, the European AIDS Society Guidelines (EACS) and the European Atherosclerosis Society (ESC/EAS)

guidelines for CVD prevention in HIV infected patients on ART. On figure 16 we can notice a discrepancy between statins recommendations of the ACC/AHA (37.9%) and the EACS (21.3%) and ESC/EAS (25.6%), current lipid lowering therapies recommendations for eligibility should therefore be applied with caution in the HIV-infected population. But still, this prevalence of lipid-lowering indication is significantly high in all considered models!

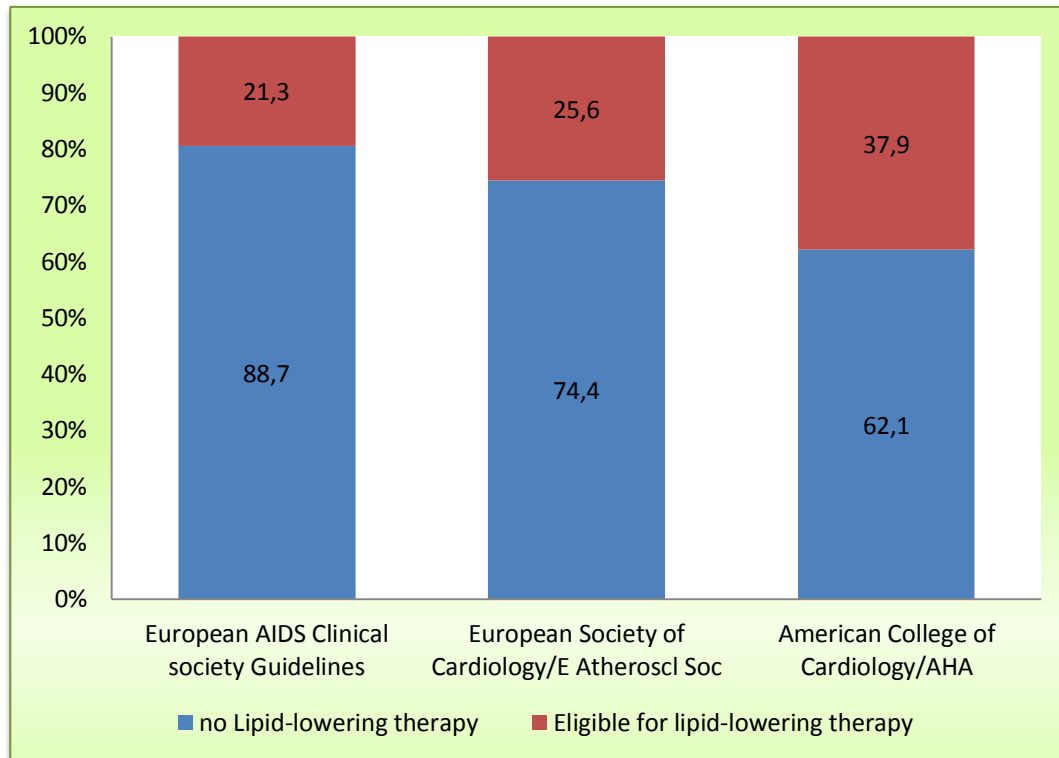


Figure 16: Prevalence of Lipid-lowering therapy eligibility.

Conclusion

The HIV-treated population of Croatia combines a constellation of significantly prevalent individual risk factors:

- **42% are current smokers!**
- **23% are hypertensive.**
- **34% have Hypercholesterolemia (>6.2 mmol/L).**
- **38% of patients are overweight.**
- **12% are obese.**

- 27% exhibit metabolic syndrome.
- 7.8% of patients suffered past cardiovascular event.
- 12.9% patients have a family history of premature cardiovascular event.
- 21% of patients are already treated for high blood pressure.
- 18.4% are already treated with lipid-lowering agents.
- 46% of the studied population have an abacavir-including regimen.
- 10% of patients have a detectable viral load.
- 11.6% of patients have a low CD4+ cell count.

The prevalence of compound major CVD risk factors is therefore high. All these factors synergistically interact as worsening the already cardiovascularly debilitating HIV infection per se. Preventing cardiovascular events in HIV-infected persons in Croatia should be a priority.

Management of “high-risk for CVD” HIV-infected patients

Antiretroviral treatment started on time

Because HIV replication per se directly damages the myocardium, and can worsen any CVD risk models score, the European Aids Clinical Society (EACS) recommends to initiate ART even before CD4+ cell count drops below 500 cells/ μ L.

Prevention of cardiovascular disease and lifestyle modification Cardiovascular risk in HIV patients needs to be evaluated before starting and 3 to 6 months after initiating a ART regimen. Of note, a careful selection of antiretroviral combination, (provided unlimited access to the least detrimental drugs regarding lipid and glucose metabolism) is of very first importance. Because cardiovascular risk management is necessary to counter balance the increased cardiovascular morbidity in this HIV-infected population, the interventions for cardiovascular risk reduction should follow those of the general population considered at “high risk of CVD” by any CVD

assessment models or the specific HIV-infected patients oriented CVD risk model like the DAD(R) model (see www.cphiv.dk/tools.aspx).

The modifiable risk factors should be aggressively handled towards maximum reduction: smoking status, high blood pressure, diabetes, excessive BMI, dyslipidemias; drug treatments being reserved for the subgroups where benefits are considered to outweigh potential harm.

Dyslipidemias management

Even though, the increased risk of CVD by HIV infection itself has yet to be reflected in conventional risk calculations, this increased risk is a valuable argument for lipid-lowering treatment in dyslipidemic HIV-infected patients even if this risk can be overestimated by conventional risk calculation [53]. Appropriate use of lipid-lowering drugs in these patients requires a thorough attention towards multiple drug interactions between HIV therapies and commonly used cardiovascular drugs.

The problem with statin therapy in patients receiving antiretroviral therapy is not lack of efficacy in reducing LDL-C level, but drug interactions with PIs and NNRTIs. The PIs inhibit cytochrome P450 (CYP) 3A4 isoenzymes, which metabolize some statins: Drug interactions that raise statins level, leading to potential hepatotoxicity, myopathy and rhabdomyolysis are then of particular concern for HIV-infected patients. Simvastatin and lovastatin are metabolized by CYP 3A4, thus, simvastatin or lovastatin should not be used by PI treated patients. Atorvastatin is less extensively metabolized by CYP 3A4, so a carefully monitored use is possible. Pravastatin undergoes sulfurylation and then bypasses CYP450 isoenzymes catabolic pathway. However, combined with saquinavir/ritonavir, atorvastatin was increased almost 2-fold and pravastatin was decreased by half (simvastatin was increased more than 30-fold in this study)[54]. So a cautious introduction of these two statins, atorvastatin and pravastatin is mandatory, no matter their relatively less sensible pharmacokinetic properties regarding CYP450 isoenzymes inhibitors.

Rosuvastatin is a very potent statin with a relatively lower potential for drug interactions. But some PIs increase rosuvastatin blood levels via a non-CYP3A4-related mechanism: Rosuvastatin maximum concentration was increased 4.7-fold by lopinavir/ritonavir [55] and 6-fold by atazanavir/ritonavir (most likely by increasing

rosuvastatin's oral bioavailability) [56]. Thus, high-dose rosuvastatin should be avoided by patients receiving these PIs. Interestingly no change in rosuvastatin concentration was observed with fosamprenavir/ritonavir [57].

In general, the potential for inhibition of statin metabolism is as follows: simvastatin and lovastatin > atorvastatin and rosuvastatin >> pravastatin.

Non-nucleoside reverse transcriptase inhibitors on the other hand are inducers of CYP 450 and can potentially reduce drug levels of drugs.

Efavirenz lowers simvastatin (and likely lovastatin) level by 60%, atorvastatin activity by 34%, and, paradoxically, pravastatin level by 40% (Pravastatin is cleared by the kidney so intuitively it shouldn't be influenced by drug interactions inhibiting CYP450 isoenzymes [57]. Higher levels of such statin drugs should be needed, but there is potential risk of "overdose" and would put patients at risk for rhabdomyolysis.

Delavirdine inhibits hepatic cytochrome P450 metabolism [54]. Thus, delavirdine increases statin levels and the risk of statin-related adverse effects similarly to PIs.

Modification of antiretroviral therapy

In HIV patients on ART who have had a newly developed a cardiovascular event or developed a substantial increase in cardiovascular risk, ART modification may represent an option to replace antiretroviral drugs with a risk of enhancing cardiovascular risk by more metabolic-friendly ones. Treatment modifications would include replacement of PI (especially ritonavir-boosted PI-based therapy) with non-nucleoside reverse transcriptase inhibitors (NNRTI), raltegravir or by another PI with less metabolic disturbances. Other modification could be to consider replacing stavudine, azidothymidine, or abacavir with tenofovir (see Table 1) or use a NRTI sparing regimen.

But a change in ART regimen in patients with an undetectable viral load and otherwise tolerating their current regimen well, shouldn't be an option for the only aim at preventing potential metabolic complications.

Niacin

In HIV-infected patients, niacin can decrease TG up to 32%, non HDL-cholesterol by 9% and up to 19% and increase HDL-cholesterol by 3% to 15% [58,59]. Because it can cause insulin resistance even in nondiabetic patients [58] niacin has been avoided as a first line therapy for patients using PIs, but studies in diabetic subjects suggest that this insulin resistance effect is only mild in control of glycaemia for these diabetic patients [61,62].

Fibrate

In HIV-infected patients, fibrates are not as potent as statins in preventing cardiovascular disease. Although less effective in lowering LDL-cholesterol, the ability of fibrates to increase HDL-cholesterol and to lower triglycerides levels justify their combined use with statins. Studies with HIV-1 patients treated with PI-based therapy and fibrates, including gemfibrozil, bezafibrate or fenofibrate, showed a significant reduction in the concentration of TC, TG and hypertriglyceridemia [63-65]. Fibrates appear as a suitable alternative for the treatment of dyslipidemia associated with HIV, especially in the presence of hypertriglyceridemia. The association between fibrates and statins has been used with relative safety in the general population except for the combination of statins and gemfibrozil (gemfibrozil is a potent CYP450 system inhibitor), which is not recommended [65-67]. The association has shown positive results in HIV-associated dyslipidemia, particularly for the pravastatin/fenofibrate combination which appeared safe and has promoted a significant improvement in lipid parameters [68,69]. However, Periodic monitoring of serum creatinine, creatine kinase, and transaminases should be performed for the use of fibrates [64,65,67].

Fish oil

Liver cod oil and other fish oils containing eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA) [omega-3 fatty acids] have strong anti-inflammatory and anti-platelets properties [70,71]. They restore the ratio omega-3/omega-6; ideally around 1:5 but unfortunately more often around 1:20 in the nowadays occidental (inappropriate) diet ... The rapid evolution of human diet away from a 1:5 omega-3

over omega-6 ratio, such as during the pre-intensive agriculture era has been too fast for human metabolism to adapt to such rapid changes [72]. This is commonly believed to be the reason why modern diets are correlated with many inflammatory disorders. It is now understood that inflammation is a major component in the pathogenesis of atherosclerosis [73]. Consumption of omega-3 fatty acids from marine sources lowers markers of inflammation in the blood such as C-reactive protein, interleukin 6, and TNF alpha [74]. HIV-infected patients consuming fish oil supplements have efficiently reduced their triglycerides levels [71] and associated with fenofibrate, the results on TG are additive.

Extra virgin olive oil

Even if extra virgin olive oil's fatty acids profile is quite neutral over the omega-3/omega-6 ratio, it contains a phenolic fraction that subsides inflammation. A randomized, crossover, controlled trial including 39 HIV-positive male participants using ART, has been able to show that extra virgin olive oil (compared to refined olive oil) lowers high-sensitivity C-reactive protein [75]. Other inflammatory and biological markers were monitored (interleukin-6, fibrinogen, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, malondialdehyde, glutathione-peroxidase, superoxide dismutase, oxidized LDL and von Willebrand factor) but extra virgin olive oil only lowered erythrocyte sedimentation rate (ESR) and high-sensitivity C-reactive protein (hsCRP). Anyway, in participants using lopinavir/ritonavir, ESR and hsCRP concentrations decreased 62% and 151%, respectively, after extra virgin olive oil administration suggesting that such a supplementation could be beneficial to hinder inflammatory and oxidative subclinical processes always present in HIV-infection. Even successfully treated HIV-infected patients may still have an increased cardiovascular risk, which might be related to inflammation and dyslipidemia induced by HIV and/or antiretroviral therapy. A study suggests that in patients with undetectable viral load, there is a significant association between markers of inflammation and serum levels of cholesterol and triglycerides as well as the cholesterol/HDL-cholesterol ratio [76].

Acknowledgements

Because this review will be the final point to university medical studies, I have a thankful thought to all Professors, doctors, nurses and health-care providers who have shared and transmitted their knowledge all these years.

I also wish to thank my mentor, Pr.Dr; Sc. Josip Begovac whose help, advices and contribution revealed crucial for the completion of this review.

I thank Pr.Dr; Sc Davorka Lukas and Pr.Dr; Sc Goran Tešović for having accepted being members of the evaluation committee.

References

1. **Passaes CP**, Sáez-Cirión A. HIV cure research: advances and prospects. *Virology* 2014; 454-455: 340-352 [PMID: 24636252 DOI: 10.1016/j.virol.2014.02.021]
2. **Deeks SG**, Lewin SR, Havlir DV. The end of AIDS: HIV infection as a chronic disease. *Lancet* 2013; 382: 1525-1533 [PMID: 24152939 DOI: 10.1016/S0140-6736(13)61809-7]
3. **Calvo KR**, Daar ES. Antiretroviral therapy: treatment-experienced individuals. *Infect Dis Clin North Am* 2014; 28: 439-456 [PMID: 25151565 DOI: 10.1016/j.idc.2014.06.005]
4. **Sobieszczyk ME**, Talley AK, Wilkin T, Hammer SM. Advances in antiretroviral therapy. *Top HIV Med* 2005; 13: 24-44 [PMID: 15849370]
5. **Arribas JR**, Pialoux G, Gathe J, Di Perri G, Reynes J, Tebas P, Nguyen T, Ebrahimi R, White K, Piontkowsky D. Simplification to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of ritonavir-boosted protease inhibitor with emtricitabine and tenofovir in adults with virologically suppressed HIV (STRATEGY-PI): 48 week results of a randomised, open-label, phase 3b, non-inferiority trial. *Lancet Infect Dis* 2014; 14: 581-589 [PMID: 24908551 DOI: 10.1016/S1473-3099(14)70782-0]
6. **Boesecke C**, Pett SL. Clinical studies with chemokine receptor-5 (CCR5) inhibitors. *Curr Opin HIV AIDS* 2012; 7: 456-462 [PMID: 22832708 DOI: 10.1097/COH.0b013e328356e933]
7. **Miyamoto F**, Kodama EN. Development of small molecule HIV-1 fusion inhibitors: linking biology to chemistry. *Curr Pharm Des* 2013; 19: 1827-1834 [PMID: 23092276 DOI: 10.2174/1381612811319100007]
8. **Randolph JT**, DeGoey DA. Peptidomimetic inhibitors of HIV protease. *Curr Top Med Chem* 2004; 4: 1079-1095 [PMID:15193140 DOI: 10.2174/1568026043388330]
9. **Balzarini J**. Current status of the non-nucleoside reverse transcriptase inhibitors of human immunodeficiency virus type 1. *Curr Top Med Chem* 2004; 4:921-944 [PMID: 15134549 DOI:10.2174/1568026043388420]
10. **Rigourd M**, Lanchy JM, Le Grice SF, Ehresmann B, Ehresmann C, Marquet R. Inhibition of the initiation of HIV-1 reverse transcription by 3'-azido-3'-deoxythymidine. Comparison with elongation. *J Biol Chem* 2000; 275: 26944-26951 [PMID: 10864929]
11. **Sprinz E**, Lazzaretti RK, Kuhmmer R, Ribeiro JP. Dyslipidemia in HIV infected individuals. *Braz J Infect Dis* 2010; 14: 575-588 [PMID: 21340298 DOI: 10.1016/S1413-8670(10)70115-X]
12. **Carr A**, Samaras K, Burton S, Law M, Freund J, Chisholm DJ, Cooper DA. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. *AIDS* 1998; 12: F51-F58 [PMID: 9619798 DOI: 10.1097/00002030-199807000-00003]
13. **Wohl DA**, McComsey G, Tebas P, Brown TT, Glesby MJ, Reeds D, Shikuma C, Mulligan K, Dube M, Wininger D, Huang J, Revuelta M, Currier J, Swindells S, Fichtenbaum C, Basar M, Tungsiripat M, Meyer W, Weihe J, Wanke C. Current concepts in the diagnosis and management of metabolic complications of HIV infection and its therapy. *Clin Infect Dis* 2006; 43: 645-653 [PMID: 16886161 DOI: 10.1086/507333]
14. **Carr A**, Emery S, Law M, Puls R, Lundgren JD, Powderly WG. An objective case definition of lipodystrophy in HIV-infected adults: a case-control study. *Lancet* 2003; 361: 726-735 [PMID: 12620736 DOI: 10.1016/S0140-6736(03)12656-6]

15. **Behrens GM**, Stoll M, Schmidt RE. Lipodystrophy syndrome in HIV infection: what is it, what causes it and how can it be managed? *Drug Saf* 2000; 23: 57-76 [PMID: 10915032 DOI: 10.2165/00002018-200023010]
16. **Freitas P**, Carvalho D. Lipodystrophy: beyond generalization? *Panminerva Med* 2013; 55: 253-268 [PMID: 24088799]
17. **Grunfeld C**. Dyslipidemia and its Treatment in HIV Infection. *Top HIV Med* 2010; 18: 112-118 [PMID: 20921577]
18. **Chan R**, Uchil PD, Jin J, Shui G, Ott DE, Mothes W, Wenk MR. Retroviruses human immunodeficiency virus and murine leukemia virus are enriched in phosphoinositides. *J Virol* 2008; 82: 11228-11238 [PMID: 18799574 DOI: 10.1128/JVI.00981-08]
19. **Campbell SM**, Crowe SM, Mak J. Virion-associated cholesterol is critical for the maintenance of HIV-1 structure and infectivity. *AIDS* 2002; 16: 2253-2261 [PMID: 12441796 DOI: 10.1097/00002030-200211220-00004]
20. **Hanley TM**, Viglianti GA. Nuclear receptor signaling inhibits HIV-1 replication in macrophages through multiple transrepression mechanisms. *J Virol* 2011; 85: 10834-10850 [PMID: 21849441 DOI: 10.1128/JVI.00789-11]
21. **Hanley TM**, Blay Puryear W, Gummuluru S, Viglianti GA. PPARgamma and LXR signaling inhibit dendritic cell-mediated HIV-1 capture and trans-infection. *PLoS Pathog* 2010; 6: e1000981 [PMID: 20617179 DOI: 10.1371/journal.ppat.1000981]
22. **Sankatsing RR**, Wit FW, Vogel M, de Groot E, Brinkman K, Rockstroh JK, Kastelein JJ, Stroes ES, Reiss P. Increased carotid intima-media thickness in HIV patients treated with protease inhibitors as compared to non-nucleoside reverse transcriptase inhibitors. *Atherosclerosis* 2009; 202: 589-595 [PMID: 18599064 DOI: 10.1016/j.atherosclerosis.2008.05.028]
23. **Wang X**, Chai H, Yao Q, Chen C. Molecular mechanisms of HIV protease inhibitor-induced endothelial dysfunction. *J Acquir Immune Defic Syndr* 2007; 44: 493-499 [PMID: 17245228 DOI: 10.1097/QAI.0b013e3180322542]
24. **Riddler SA**, Li X, Otvos J, Post W, Palella F, Kingsley L, Visscher B, Jacobson LP, Sharrett AR. Antiretroviral therapy is associated with an atherogenic lipoprotein phenotype among HIV-1-infected men in the Multicenter AIDS Cohort Study. *J Acquir Immune Defic Syndr* 2008; 48: 281-288 [PMID: 18545156 DOI: 10.1097/QAI.0b013e31817bbbf0]
25. **Rawlings ND**, Tolle DP, Barrett AJ. Evolutionary families of peptidase inhibitors. *Biochem J* 2004; 378: 705-716 [PMID: 14705960 DOI: 10.1042/BJ20031825]
26. **Qiu X**, Liu ZP. Recent developments of peptidomimetic HIV-1 protease inhibitors. *Curr Med Chem* 2011; 18: 4513-4537 [PMID: 21864279 DOI: 10.2174/092986711797287566]
27. **Hui DY**. Effects of HIV protease inhibitor therapy on lipid metabolism. *Prog Lipid Res* 2003; 42: 81-92 [PMID: 12547652 DOI: 10.1016/S0163-7827(02)00046-2]
28. **Riddler SA**, Li X, Chu H, Kingsley LA, Dobs A, Evans R, Palella F, Visscher B, Chmiel JS, Sharrett A. Longitudinal changes in serum lipids among HIV-infected men on highly active antiretroviral therapy. *HIV Med* 2007; 8: 280-287 [PMID: 17561873 DOI: 10.1111/j.1468-1293.2007.00470.x]
29. **Patick AK**, Potts KE. Protease inhibitors as antiviral agents. *Clin Microbiol Rev* 1998; 11: 614-627 [PMID: 9767059]
30. **Arribas JR**, Pulido F, Delgado R, Lorenzo A, Miralles P, Arranz A, González-García JJ, Cepeda C, Hervás R, Paño JR, Gaya F, Carcas A, Montes ML, Costa JR, Peña JM. Lopinavir/ritonavir as single-drug therapy for maintenance of HIV-1 viral suppression: 48-week results of a randomized, controlled, open-label, proof-of-concept pilot clinical trial (OK Study). *J Acquir Immune Defic Syndr* 2005; 40: 280-287 [PMID: 16249701 DOI: 10.1097/01.qai.0000180077.59159.f4]
31. **Carr A**, Hudson J, Chuah J, Mallal S, Law M, Hoy J, Doong N, French M, Smith D, Cooper DA. HIV protease inhibitor substitution in patients with lipodystrophy: a randomized, controlled, open-label, multicentre study. *AIDS* 2001; 15: 1811-1822 [PMID: 11579243 DOI: 10.1097/00002030-200109280-00010]
32. **Helleberg M**, Kronborg G, Larsen CS, Pedersen G, Pedersen C, Nielsen L, Laursen A, Obel N, Gerstoft J. Decreasing rate of multiple treatment modifications among individuals who initiated antiretroviral therapy in 1997-2009 in the Danish HIV Cohort Study. *Antivir Ther* 2012; Epub ahead of print: [PMID: 23072939 DOI: 10.3851/IMP436]
33. **Prosperi MC**, Fabbiani M, Fanti I, Zaccarelli M, Colafigli M, Mondì A, D'Avino A, Borghetti A, Cauda R, Di Giambenedetto S. Predictors of first-line antiretroviral therapy discontinuation due to drug-related adverse events in HIV-infected patients: a retrospective cohort study. *BMC Infect Dis* 2012; 12: 296 [PMID: 23145925 DOI: 10.1186/1471-2334-12-296]

34. **Sabin CA**, Worm SW, Weber R, Reiss P, El-Sadr W, Dabis F, De Wit S, Law M, D'Arminio Monforte A, Friis-Møller N, Kirk O, Pradier C, Weller I, Phillips AN, Lundgren JD. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the d:A:D study: a multi-cohort collaboration. *Lancet* 2008;371:1417–1426 [PMID: 18387667 PMCID: PMC2688660 DOI: 10.1016/S0140-6736(08)60423-7]
35. **Herskowitz A**, Willoughby SB, Baughman KL, Schulman SP, Bartlett JD. Cardiomyopathy associated with antiretroviral therapy in patients with HIV infection: a report of six cases. *Ann Intern Med* 1992;116:311–313 [PMID: 1733387]
36. **Tanuma J**, Ishizaki A, Gatanaga H, Kikuchi Y, Kimura S, Hiroe M, Oka S. Dilated cardiomyopathy in an adult human immunodeficiency virus type 1-positive patient treated with a zidovudine-containing antiretroviral regimen. *Clin Infect Dis* 2003; 37:e109–e111 [PMID: 13130421 DOI: 10.1086/377609]
37. **Jacob AJ**, Sutherland GR, Bird AG, Brettle RP, Ludlam CA, McMillan A, Boon NA. Myocardial dysfunction in patients infected with HIV: prevalence and risk factors. *Br Heart J* 1992;68:549–553 [PMID: 1334683 PMCID: PMC1025683]
38. **Cardoso JS**, Moura B, Martins L, Mota-Miranda A, Rocha Goncalves F, Lecour H. Left ventricular dysfunction in human immunodeficiency virus (HIV)-infected patients. *Int J Cardiol* 1998;63:37–45 [PMCID: PMC3734877 DOI: 10.5830/CVJA-2012-048]
39. **Cardoso JS**, Moura B, Mota-Miranda A, Goncalves FR, Lecour H. Zidovudine therapy and left ventricular function and mass in human immunodeficiency virus-infected patients. *Cardiology* 1997;88:26–28.
40. **DAD Study Group, Friis-Møller N**, Reiss P, Sabin CA, Weber R, Monforte Ad, El-Sadr W, Thiébaud R, De Wit S, Kirk O, Fontas E, Law MG, Phillips A, Lundgren JD. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med*. 2007 Apr 26;356(17):1723-35 [PMID: 17460226 DOI: 10.1056/NEJMoa062744]
41. **Thienemann F**, Sliwa K, Rockstroh JK. HIV and the heart: the impact of antiretroviral therapy: a global perspective. *Eur Heart J*. 2013 Dec;34(46):3538-46 [PMID: 24126882 DOI: 10.1093/eurheartj/ehs388]
42. **Berry C**, Tardif JC, Bourassa MG. Coronary heart disease in patients with diabetes: part I: recent advances in prevention and noninvasive management. *J Am Coll Cardiol* 2007;49:631–642. Epub 2007 Jan 26 [PMID: 17291928 DOI: 10.1016/j.jacc.2006.09.046]
43. **Butt AA**, Fultz SL, Kwok CK, Kelley D, Skanderson M, Justice AC. Risk of diabetes in HIV infected veterans pre- and post-HAART and the role of HCV coinfection. *Hepatology* 2004;40:115–119 [PMID:15239093 DOI: 10.1002/hep.20289]
44. **Brown TT**, Cole SR, Li X, Kingsley LA, Palella FJ, Riddler SA, Visscher BR, Margolick JB, Dobs AS. Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter aids cohort study. *Arch Intern Med* 2005;165:1179–1184 [PMID: 15911733 DOI: 10.1001/archinte.165.10.1179]
45. **Brown TT**, Glesby MJ. Management of the metabolic effects of HIV and HIV drugs. *Nat Rev Endocrinol* 2012;8:11–21 [PMID: 21931374 PMCID: PMC3371609 DOI: 10.1038/nrendo.2011.151]
46. **Grunfeld C**. Insulin resistance in HIV infection: drugs, host responses, or restoration to health? *Topics HIV Med* 2008;16:89–93 [PMID: 18591716]
47. **Blumer RM**, van Vonderen MG, Sutinen J, Hassink E, Ackermans M, van Agtmael MA, Yki-Jarvinen H, Danner SA, Reiss P, Sauerwein HP. Zidovudine/lamivudine contributes to insulin resistance within 3 months of starting combination antiretroviral therapy. *AIDS (London, England)* 2008;22:227–236 [PMID: 18097225 DOI: 10.1097/QAD.0b013e3282f33557]
48. **Fleischman A**, Johnsen S, Systrom DM, Hrovat M, Farrar CT, Frontera W, Fitch K, Thomas BJ, Torriani M, Cote HC, Grinspoon SK. Effects of a nucleoside reverse transcriptase inhibitor, stavudine, on glucose disposal and mitochondrial function in muscle of healthy adults. *Am J Physiol Endocrinol Metab* 2007;292: E1666–E1673 [PMID: 17284576 PMCID: PMC3206591 DOI: 10.1152/ajpendo.00550.2006]
49. **Lorgis L**, Cottenet J, Molins G, Benzenine E, Zeller M, Aube H, Touzery C, Hamblin J, Gudjoncik A, Cottin Y, Quantin C. Outcomes after acute myocardial infarction in HIV-infected patients: analysis of data from a French nationwide hospital medical information database. *Circulation* 2013;127:1767–1774 [PMID: 23543004 DOI: 10.1161/CIRCULATIONAHA.113.001874]
50. **Lichtenstein KA**, Armon C, Buchacz K, Chmiel JS, Buckner K, Tedaldi EM, Wood K, Holmberg SD, Brooks JT; HIV Outpatient Study (HOPS) Investigators. Low CD4+ T cell count is a risk factor for cardiovascular disease events in the HIV outpatient study. *Clin Infect Dis*. 2010 Aug 15;51(4):435-47 [PMID: 20597691 DOI: 10.1086/655144]
51. **Lang S**, Mary-Krause M, Simon A, Partisani M, Gilquin J, Cotte L, Boccara F, Costagliola D; French Hospital Database on HIV (FHDH)–ANRS CO4. HIV replication and immune status are independent predictors of the

- risk of myocardial infarction in HIV-infected individuals. *Clin Infect Dis*. 2012 Aug;55(4):600-7 [PMID: 22610928 DOI: 10.1093/cid/cis489]
52. **Grunfeld C**, Delaney JA, Wanke C, Currier JS, Scherzer R, Biggs ML, Tien PC, Shlipak MG, Sidney S, Polak JF, O'Leary D, Bacchetti P, Kronmal RA. Preclinical atherosclerosis due to HIV infection: carotid intima-medial thickness measurements from the FRAM study. *AIDS*. 2009 Sep 10;23(14):1841-9 [PMID: 19455012 PMCID: PMC3156613 DOI: 10.1097/QAD.0b013e32832d3b85]
 53. **Begovac J**, Dragović G, Višković K, Kušić J, Perović Mihanović M, Lukas D, Jevtović Đ. Comparison of four international cardiovascular disease prediction models and the prevalence of eligibility for lipid lowering therapy in HIV infected patients on antiretroviral therapy. *Croat Med J*. 2015 Feb;56(1):14-23 [PMID: 25727038 PMCID: PMC4364353]
 54. **Fichtenbaum CJ**, Gerber JG. Interactions between antiretroviral drugs and drugs used for the therapy of the metabolic complications encountered during HIV infection. *Clin Pharmacokinet*. 2002;41(14):1195-211 [PMID: 12405866 DOI: 10.2165/00003088-200241140-00004]
 55. **Kiser JJ**, Gerber JG, Predhomme JA, Wolfe P, Flynn DM, Hoody DW. Drug/Drug interaction between lopinavir/ritonavir and rosuvastatin in healthy volunteers. *J Acquir Immune Defic Syndr*. 2008 Apr 15;47(5):570-8 [PMID: 18176327 DOI: 10.1097/QAI.0b013e318160a542]
 56. **Busti AJ**, Bain AM, Hall RG 2nd, Bedimo RG, Leff RD, Meek C, Mehvar R. Effects of atazanavir/ritonavir or fosamprenavir/ritonavir on the pharmacokinetics of rosuvastatin. *J Cardiovasc Pharmacol*. 2008 Jun;51(6):605-10 [PMID: 18520949 DOI: 10.1097/FJC.0b013e31817b5b5a]
 57. **Gerber JG**, Rosenkranz SL, Fichtenbaum CJ, Vega JM, Yang A, Alston BL, Brobst SW, Segal Y, Aberg JA; AIDS Clinical Trials Group A5108 Team. Effect of efavirenz on the pharmacokinetics of simvastatin, atorvastatin, and pravastatin: results of AIDS Clinical Trials Group 5108 Study. *J Acquir Immune Defic Syndr*. 2005 Jul 1;39(3):307-12 [PMID: 15980690]
 58. **Dubé MP**, Wu JW, Aberg JA, Deeg MA, Alston-Smith BL, McGovern ME, Lee D, Shriver SL, Martinez AI, Greenwald M, Stein JH; AIDS Clinical Trials Group A5148 Study Team. Safety and efficacy of extended-release niacin for the treatment of dyslipidaemia in patients with HIV infection: AIDS Clinical Trials Group Study A5148. *Antivir Ther*. 2006;11(8):1081-9 [PMID: 17302378 PMCID: PMC2288649]
 59. **Gerber MT**, Mondy KE, Yarasheski KE, Drechsler H, Claxton S, Stoneman J, DeMarco D, Powderly WG, Tebas P. Niacin in HIV-infected individuals with hyperlipidemia receiving potent antiretroviral therapy. *Clin Infect Dis*. 2004 Aug 1;39(3):419-25 [PMID: 15307011 DOI: 10.1086/422144]
 60. **Garg A**, Grundy SM. Nicotinic acid as therapy for dyslipidemia in non insulin-dependent diabetes mellitus. *JAMA* 1990; 264:723–6 [PMID: 2374275]
 61. **Grundy SM**, Vega GL, McGovern ME, et al. Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of niaspan trial. *Arch Intern Med* 2002; 162:1568–76 [PMID: 12123399]
 62. **Van JT**, Pan J, Wasty T, Chan E, Wu X, Charles MA. Comparison of extended-release niacin and atorvastatin monotherapies and combination treatment of the atherogenic lipid profile in diabetes mellitus. *Am J Cardiol* 2002; 89:1306–8 [PMID: 12031735]
 63. **Thomas JC**, Lopes-Virella MF, Del Bene VE, Cerveny JD, Taylor KB, McWhorter LS, Bultemeier NC. Use of fenofibrate in the management of protease inhibitor-associated lipid abnormalities. *Pharmacotherapy* 2000; 20: 727-734 [PMID: 10853629 DOI: 10.1592/phco.20.7.727.35179]
 64. **Calza L**, Manfredi R, Chiodo F. Statins and fibrates for the treatment of hyperlipidaemia in HIV-infected patients receiving HAART. *AIDS* 2003; 17: 851-859 [PMID: 12660532 DOI: 10.1097/00002030-200304110-00010]
 65. **Visnagarwala F**, Maldonado M, Sajja P, Minihan JL, Rodriguez-Barradas MC, Ong O, Lahart CJ, Hasan MQ, Balasubramanyam A, White AC. Lipid lowering effects of statins and fibrates in the management of HIV dyslipidemias associated with antiretroviral therapy in HIV clinical practice. *J Infect* 2004; 49: 283-290 [PMID: 15474625 DOI: 10.1016/j.jinf.2003.09.006]
 66. **Keech A**, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesäniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005; 366: 1849-1861 [PMID: 16310551 DOI: 10.1016/S0140-6736(05)67667-2]
 67. **Miller J**, Brown D, Amin J, Kent-Hughes J, Law M, Kaldor J, Cooper DA, Carr A. A randomized, double-blind study of gemfibrozil for the treatment of protease inhibitor-associated hypertriglyceridaemia. *AIDS* 2002; 16: 2195-2200 [PMID: 12409741 DOI: 10.1097/00002030-200211080-00012]

68. **Nolan DP**, O'Connor MB, O'Connor C, Moriarty M, O'Leary A, Bergin C. HIV-associated dyslipidaemia among HIV antibodypositive patients in Ireland: prevalence and management strategies. *Int J STD AIDS* 2010; 21: 75-76 [PMID: 19884356 DOI: 10.1258/ijsa.2009.009364]
69. **Aberg JA**, Zackin RA, Brobst SW, Evans SR, Alston BL, Henry WK, Glesby MJ, Torriani FJ, Yang Y, Owens SI, Fichtenbaum CJ. A randomized trial of the efficacy and safety of fenofibrate versus pravastatin in HIV-infected subjects with lipid abnormalities: AIDS Clinical Trials Group Study 5087. *AIDS Res Hum Retroviruses* 2005; 21: 757-767 [PMID: 16218799 DOI: 10.1089/aid.2005.21.757]
70. **Schmidt EB**. Marine N-3 polyunsaturated fatty acids and coronary heart disease: come a long way but expect more. *Cell Mol Biol (Noisy-le-grand)* 2010; 56: 1-3 [PMID: 20225403]
71. **Gerber JG**, Kitch DW, Fichtenbaum CJ, Zackin RA, Charles S, Hogg E, Acosta EP, Connick E, Wohl D, Kojic EM, Benson CA, Aberg JA. Fish oil and fenofibrate for the treatment of hypertriglyceridemia in HIV-infected subjects on antiretroviral therapy: results of ACTG A5186. *J Acquir Immune Defic Syndr* 2008; 47: 459-466 [PMID: 17971707 DOI: 10.1097/QAI.0b013e31815bace2]
72. **DeFilippis AP**, Sperling LS. Understanding omega-3's. *Am Heart J.* 2006 Mar;151(3):564-70 [PMID: 16504616 DOI: 10.1016/j.ahj.2005.03.051]
73. **Curtiss LK**. Reversing atherosclerosis? *N Engl J Med.* 2009 Mar 12;360(11):1144-6 [PMID: 19279347 DOI: 10.1056/NEJMcibr0810383]
74. **Li K**, Huang T, Zheng J, Wu K, Li D. Effect of marine-derived n-3 polyunsaturated fatty acids on C-reactive protein, interleukin 6 and tumor necrosis factor α : a meta-analysis. *PLoS One.* 2014 Feb 5;9(2):e88103 [PMID: 24505395 PMCID: PMC3914936 DOI: 10.1371/journal.pone.0088103]
75. **Kozić Dokmanović S**, Kolovrat K, Laškaj R, Jukić V, **Vrkić N**, **Begovac J**. Effect of Extra Virgin Olive Oil on Biomarkers of Inflammation in HIV-Infected Patients: A Randomized, Crossover, Controlled Clinical Trial. *Med Sci Monit.* 2015 Aug 16;21:2406-13 [PMID: 26280823 PMCID: PMC4544351 DOI: 10.12659/MSM.893881]
76. **Viskovic K**, Zidovec-Lepej S, Gorenec L, Grgic I, Lukas D, Zekan S, Dragobratovic A, Begovac J. Cardiovascular markers of inflammation and serum lipid levels in HIV-infected patients with undetectable viraemia. *J Int AIDS Soc.* 2014 Nov 2;17(4 Suppl 3):19548 [PMID: 25394055 PMCID: PMC4224813]

Biography

Born on the atlantic coast of France where he spent his educational years till his graduation in Master of clinical psychology, the author has then had the opportunity to complete his medical education at the medical university of Zagreb.