JMS2025;Vol8(1):93-105
UDK: 616.98:578.828.7]-085.281.8}:616-00
https://doi.org/10.55302/JMS258193jp

ASSOCIATED RISK FACTORS AND PREVALENCE OF METABOLIC SYNDROME IN PEOPLE LIVING WITH HIVAND RECEIVING ANTIRETROVIRAL TREATMENT

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Abstract

Introduction The extended life expectancy of people living with HIV infection increases the risk of metabolic syndrome (MS).

Aim To assess the prevalence of MS, the association of triple regimen antiretroviral therapy (ART) and the role of the chronic inflammatory process caused by the HIV virus with the onset of MS.

Material and methods A prospective cross-sectional study was conducted on 141 HIV infected adult patients with confirmed HIV infection who regularly receive ART at the University Clinic for Infectious Diseases and Febrile Conditions in Skopje. In all patients, the presence of MS was determined according to the criteria of the National Cholesterol Education Program Adult Treatment Panel ATP III (NCEP ATPIII) 2005. The statistical software SPSS (ver. 23.0; IBM, SPSS, USA) was used for statistical analysis.

Results The prevalence rate of MS in persons with HIV infection in RNM was 17.96%. The group of patients with MS were significantly older and had significantly higher body mass index and greater waist circumference (28.82 ± 4.6 kg/m^2 *vs.* 23.91 ± 3.6 kg/m^2, $p<0.0001$) and (101.04 ± 12.4 *vs.* 87.19 ± 9.8 cm, $p<0.0001$), respectively. Treatment of patients with ART did not show a significant difference in the group with and without MS. There was a significant difference regarding the frequency of IL 6 ($p=0.012$).

Conclusion Aging and increasing body mass index are significant risk factors for the development of MS in persons with HIV infection who are receiving ART.

Keywords: metabolic syndrome, HIV infection, antiretroviral treatment

Introduction

People living with HIV infection today have the opportunity to receive effective antiretroviral therapy (ART) that enables suppression of viral replication and immune reconstitution. ART has allowed a fatal disease to become a chronic infectious disease requiring lifelong treatment. Long-term toxicities that result from constant exposure to ART represent a challenge for the proper management of HIV infection.[1] Antiretroviral drugs and their association with the development of metabolic complications have become a major challenge for clinicians in the management of ART [2].

In 2023, globally, 77% (61-89%) of people living with HIV received ART [3]. According to the recommendations of the European AIDS Clinical Society (EACS guidelines, 12.0 October 2023), ART is recommended for all adults with HIV infection, regardless of the number of CD4 cells and the clinical stage of the disease [4].

The EACS recommendations include a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) and one integrase inhibitor (INSTI) and two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) as first-line treatment [4].

HIV infection and ART can cause the appearance of lipodystrophy, insulin resistance and dyslipidemia, which are risk factors for the development of metabolic syndrome [5].

Metabolic syndrome (MS) consists of a group of risk factors, such as hypertension, abdominal obesity, dyslipidemia and insulin resistance, which significantly increase the risk of cardiovascular diseases and diabetes mellitus. The most commonly used definitions for determining the prevalence of MS are those by the National Cholesterol Education Program Adult Treatment Panel III 2005 (NCEP ATP-III), and by the International Diabetes Federation (IDF) [5].

The prevalence of MS varies in different regions of the world and depends on the definition of MS criteria, population characteristics, study design and sample of subjects. The prevalence rate of MS in people living with HIV globally ranges from 7% to 52% [6].

A meta-analysis from 2016 showed that, depending on the criteria used the prevalence of MS, according to the definition of NCEP ATP III-2001, was: 16.7%, IDF-2005: 18%, ATP III 2004-2005: 24.6%, modified ATP III-2005: 27.9%, JIS-2009: 29.6%, and according to the European Group for the Study of Insulin Resistance EGIR: 31.3%.[7]

As stated by some criteria, the prevalence was shown to be significantly higher in women compared to men and in persons receiving ART compared to those HIV infected persons not receiving ART (ATP III 2001 18.4% *vs.* 11.8% p=0.001) [7].

Significant variations in the prevalence depending on age, disease duration, severity of infection, NNRTI use, and time of the study publication have also been shown [7].

The pathogenesis of MS is multifactorial. Aging, genetic individual characteristics, traditional social influences and behavioral risk factors play an important role in the onset of MS. The HIV virus itself, that is, HIV viral replication and immune dysregulation, results in a chronic systemic inflammatory response that increases the risk of developing cardiovascular and metabolic diseases in people with HIV infection [8].

In a large randomized clinical trial comparing continuous *versus* intermittent treatment with ART (SMART study), stopping or not starting ART was associated with an increased risk of cardiovascular diseases, which suggested that any of these HIV-associated factors, such as viral replication, immunodeficiency, and inflammation may be associated with the occurrence of a cardiovascular disease [9].

There are studies showing an increase in the incidence of MS in people living with HIV who are on ART compared to people living with HIV, ART naïve, suggesting that ART may be a risk factor for MS [6].

Data are presented on the role of the integrase inhibitor dolutegravir (DTG) suggesting weight gain in individuals starting DTG-based treatment. Dolutegravir is a drug that is the first line of treatment as recommended by EACS and WHO due to its efficacy, high genetic resistance barrier and low potential of side effects of therapy. Two randomized studies in Sub-Saharan Africa have shown that DTG causes significant weight gain in treatment-naïve individuals after initiation of DTG treatment, which subsequently increases the risk of developing MS [10].

Doravirine (DOR) is the last of the NNRTI group, introduced in the treatment of patients with HIV infection and, like DTG, represents the first line of treatment. The results of the randomized active-controlled, double-blind phase 3 study DRIVE AHEAD and of the multicenter study DRIVE FORWARD show that the DOR-based regimen has a positive effect on the lipid profile and the onset of MS [11].

Differences in the prevalence of MS in people living with HIV in different countries impose the need for regional assessment of the prevalence of MS in our country. The components of MS are clearly defined in the definition of MS, but it is important to assess the influence of various factors, such as age, sociodemographic characteristics, the role of the chronic inflammatory process caused by the HIV virus as well as different regimens of ART, in the prediction of individuals at high risk for MS. These individuals could then be targeted for intervention and therapy. Such an approach would enable the selection of preventive programs and measures to prevent the occurrence of MS, as well as the selection of the safest and most effective ART treatment, which would improve the quality of life of people living with HIV.

Aim

- To estimate the prevalence of MS in people living with HIV infection who are on ART treatment.
- To assess the association of triple ART regimen with two nucleoside reverse transcriptase inhibitors (NRTI) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) and a triple ART regimen with two nucleoside reverse transcriptase inhibitors (NRTI) and one integrase inhibitor (INSTI) on the onset of MS in people living with HIV infection and who regularly receive ART.
- To assess the role of the chronic inflammatory process caused by the HIV virus in the development of MS.

Material and methods

A prospective cross-sectional study of demographic, clinical, anthropometric and laboratory biochemical data was performed on 141 HIV-infected adult patients (>18 years), with confirmed HIV infection. HIV infection is confirmed by determining the viral load of HIV RNA in human plasma, while the degree of immune deficiency by determining the number of CD4 cells. We analyzed patients who were regularly monitored at the University Clinic for Infectious Diseases and Febrile Conditions in Skopje, Republic of North Macedonia, and regularly received ART in the period from October 2023 to October 2024.

Persons with HIV infection who were under 18 years of age, pregnant women, persons who had previously received pre-exposure or post-exposure prophylaxis for HIV, and persons with active opportunistic infection or cancer were excluded from the study.

The criteria for starting and implementing ART were according to the recommendations of the European AIDS clinical society (EACS guidelines 12.0 October 2023).

The tests carried out during the study were not in conflict with the ethical principles of the Helsinki Declaration. Each involved patient received information about the study in written form and signed a consent to participate in the study. Consent to conduct the study was also requested from the Ethics Committee of the Faculty of Medicine in Skopje.

In all patients, the presence of MS was determined according to the criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) 2005, defined by at least three risk factors out of a total of five, namely:

1. low levels of HDL (high density lipoprotein cholesterol) (<1 mmol/l or 40 mg/dl for men and < 1.3 mmol/l or 50 mg/dl for women),
2. increased waist circumference (>102 cm for men, >88 cm, for women),
3. hypertriglyceridemia (>1.7 mmol/l or 150 mg/dl),
4. increased levels of fasting glucose (>5.6 mmol/l or 100 mg/dl), and
5. hypertension (systolic >130 mmHg or diastolic >85 mmHg). [12]

Sociodemographic variables such as gender, age, smoking, and alcohol consumption were taken from the patient's medical history during outpatient visits for controlling the HIV infection.

Physical examinations to determine the presence of MS in persons with HIV infection were performed in two consecutive measurements over a period of 6 months. Blood pressure was measured with a mercury pressure device with a standard cuff, with a reference value for systolic pressure of 130 mmHg, and for diastolic pressure 85 mmHg. Elevated blood pressure was considered as an increase in either systolic or diastolic blood pressure values. Blood pressure was measured after the patient had rested (seated in a chair) for at least 5 minutes, with their feet flat on the floor. The measurement was performed on the left hand (upper arm). Blood pressure values were calculated as the mean of two consecutive measurements as recommended by the Joint National Committee (JNC7) [13].

Body weight was determined by measuring body weight with a scale, expressed in kilograms. Waist circumference and hip circumference were measured with a metronome expressed in centimeters.

In order to determine the body mass index (BMI), a calculator was used by entering each patient's body height, weight, age and gender. The obtained values were interpreted as: underweight <18.5, normal weight 18.5-25, overweight 25-30, obese >30.

Blood samples were collected from patients during two consecutive visits, 6 months apart, after at least 8 hours of fasting, in a total amount of 16.5 ml of blood drawn in three tubes BD Vacutainer CAT (Clot Activator tube) - 6 ml for determination of HDL cholesterol, LDL cholesterol, total cholesterol and triglycerides and fasting glucose, C-reactive protein (ref. values 1-5 mg/l) and interleukin 6 (ref. values <7 pg/ml); Bd Vacutainer PPT K2E 15.8 ml for determining HIV RNA viral load in human plasma and BD Vacutainer K2E 3.6 ml for determining the number of CD4 cell/ml. Blood samples for laboratory biochemical investigations were analyzed immediately after blood collection in the laboratory of the University Clinic for Infectious Diseases and Febrile Conditions in Skopje with standard laboratory biochemical tests.

Quantification of HIV RNA levels in human plasma was performed at the University Clinic for Infectious Diseases and Febrile Conditions using the real-team polymerase chain reaction (RT-PCR COBAS AMPLI Prep-COBAS TaqMan 48 Roche with lower limit detection <20 cop/ml, Abbot System m2000sp/m2000rt with lower limit of detection <40 cop/ml and GeneXpert with lower limit of detection <40 cop/ml), whereby undetectable values of HIV RNA in serum were defined as <40 cop.ml. A detectible level of HIV RNA in serum was defined as >200 cop/ml.

Virologic failure was defined as serum HIV RNA > 1000 cop/ml. Immunological deficiency was determined by absolute photomicroscopy and light absorption detection on a multicolor platform (Facs Presto-BD) for absolute and percentage detection of CD4 lymphocytes, expressed in the number of cells per milliliter (cell/ml). Each sample was analyzed with a separate cartridge. Persons with HIV infection with immunodeficiency were defined as persons with HIV infection with a CD4 count <350 cell/ml (late presenters <350 cell/ml).

All patients were on a triple regimen of ART in the following two combinations as recommended by the European AIDS clinical society (EACS guidelines 12.0 October 2023): two nucleoside reverse transcriptase inhibitors (NRTIs): tenofovir disoproxil fumarate/emtricitabine, abacavir/lamivudine, tenofovir alafenamide/emtricitabine in combination with one non-nucleoside reverse transcriptase inhibitor (NNRTI) doravirine, efavirenz, rilpivirine, or one integrase inhibitor (INSTI) raltegravir, dolutegravir, bictegravir.

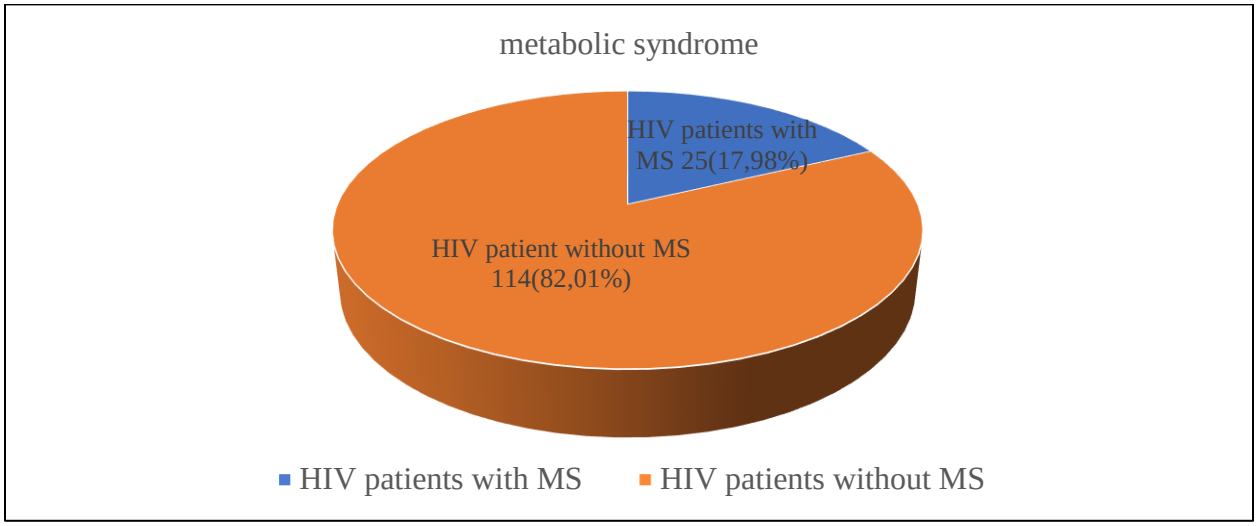
Results

The study included 141 adult patients with confirmed HIV infection, determined by the presence of HIV RNA viral load in human plasma, who were on ART for more than 3 months. Two patients were excluded during the study, one due to verification of T cell lymphoma, and the other one due to verification of lung tumor.

The prevalence of MS syndrome was determined based on the criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), that is, the presence of at least three of the five analyzed risk factors. Twenty-five patients had MS, which means that the prevalence was 17.96%.

Two groups of patients were defined - the first group of HIV-infected patients with MS (n=25), and the second group of HIV-infected patients without MS (n=114) who were on ART for more than 3 months (Figure 1).

Figure 1. Prevalence of metabolic syndrome in people living with HIV and who were on ART for more than 3 months in RNM



Patients with and without metabolic syndrome did not differ significantly in terms of gender (p=0.29); men constituted the majority of the groups with and without metabolic syndrome (92% and 96.49%, respectively). Patients with metabolic syndrome were significantly older (41.7 ± 9.1 *vs*. 37.4 ± 8.3,

p=0.023). 32% of patients with and 44.25% without MS were smokers; 3.57% of patients without MS consumed alcohol. Smoking status and frequency of alcohol consumption were not significantly different between groups with and without MS (p=0.26 and p=0.56, respectively).

The average body mass index was 28.82 ± 4.6 kg/m^2 in the group with MS, 23.91 ± 3.6 kg/m^2 in the group without MS. The difference of 4.91 kg/m^2 was statistically significant (p<0.0001).

Patients with MS had significantly greater waist circumference (101.04 ± 12.4 *vs*. 87.19 ± 9.8 cm, p<0.0001) and hip circumference (105.84 ± 9.1 *vs*. 98.73 ± 7.7, p=0.000081). An increased waist circumference was measured significantly more frequently in patients with MS (44% *vs*. 4.39%, p<0.0001) (Table 1).

Table 1. Sociodemographic factors affecting the development of MS in patients with HIV infection who were on ART for more than 3 months in RNM

variable		Metabolic syndrome			p-level
		n	yes N=25	no N=114	
Gender n(%)	women	6	2 (8)	4 (3.51)	Fisher´s exact p=0.29
	men	133	23 (92)	110 (96.49)	
Age	mean ± SD		41.7 ± 9.1	37.4 ± 8.3	t=2.3 *p=0.023
	min- max		26 – 58	21 – 57	
Smokers n(%)	yes	58	8 (32)	50 (44.25)	X^2=1.3 p=0.26
	no	80	17 (68)	63 (55.75)	
Alcohol n(%)	yes	4	0	4 (3.57)	Fisher´s exact p=0.56
	no	40	11 (44)	29 (25.89)	
	often	2	0	2 (1.79)	
	occasionally	91	14 (56)	77 (68.75)	
BMI (kg/m^2)	mean ± SD		28.82 ± 4.6	23.91 ± 3.6	t=5.8 ***p=0.000000
	min- max		22.6 – 40.1	16.2 – 36.5	
Waist circumference (cm) n(%)	mean ± SD		101.04 ± 12.4	87.19 ± 9.8	t=6.1 ***p=0.000000
	min- max		84 – 130	63 – 125	
	normal	123	14 (56)	109 (95.61)	X^2=31.6 ***p=0.000000
	high	16	11 (44)	5 (4.39)	
Hip circumference (cm)	mean ± SD		105.84 ± 9.1	98.73 ± 7.7	t=4.1 ***p=0.000081
	min- max		90 – 120	79 – 136	

t (Student t-test), X^2(Chi-square test)

*sig p<0.05, ***sig p<0.0001

According to the results shown in Table 2, patients with and without MS differed significantly in terms of the frequency of high blood pressure (p<0.0001), in terms of the levels of glycemia, triglycerides, HDL (p<0.0001) and IL-6 (p=0.012).

Blood pressure was elevated in 80% of patients with MS and 35.96% of patients without MS.

Glycemia was significantly higher in the group with MS (6.35 ± 1.1 *vs*. 5.45 ± 0.5 mmol/L); increased glycemic levels were registered significantly more often in the group with MS (32% *vs*. 6.14%).

Significantly higher triglycerides were measured in the group with MS (2.67 ± 1.1 *vs*. 1.20 ± 0.6 mmol/L), and significantly lower levels of HDL (0.93 ± 0.2 *vs*. 1.24 ± 0.3 mmol/L); 60% of patients with and 8.77% of patients without MS had elevated triglycerides, 72% of patients with and 9.65% of patients without MS had reduced HDL levels.

Table 2. Criteria for the onset of metabolic syndrome

variable		Metabolic syndrome			p-level
		n	yes N=25	no N=114	
TA	normal	78	5 (20)	73 (64.04)	X^2=16.1
	high	61	20 (80)	41 (35.96)	***p=0.000059
CD4	mean ± SD		637.20 ± 304.4	659.18 ± 321.6	t=0.31
	min- max		90 – 1205	6 – 1679	p=0.755
	low	19	5 (20)	14 (12.28)	Fisher´s exact
	normal	120	20 (80)	100 (87.72)	p=0.337
HIV RNA	low	1	0	1 (0.88)	
	normal	135	23 (92)	112 (98.25)	
	high	3	2 (8)	1 (0.88)	
glucose mmol/L	mean ± SD		6.35 ± 1.1	5.45 ± 0.5	t=6.1
	min- max		4.8 – 9.3	4.3 – 6.9	***p=0.0000000
	normal	124	17 (68)	107 (93.86)	***p=0.00103
	high	15	8 (32)	7 (6.14)	
CRP	mean ± SD		3.84 ± 3.5	3.13 ± 8.2	Z=0.42
	min- max		1 – 12	1 – 74	p=0.67
	median (IQR)		2 (1 – 6)	1 (1 – 2)	
	normal	133	24 (96)	109 (95.61)	p=1.0
	high	6	1 (4)	5 (4.39)	
triglycerides mmol/L	mean ± SD		2.67 ± 1.1	1.20 ± 0.6	t=8.8
	min- max		1.03 – 5.24	0.4 – 4.14	***p=0.000000
	normal	114	10 (40)	104 (91.23)	X^2=36.48
	high	25	15 (60)	10 (8.77)	***p=0.000000
cholesterol mmol/L	mean ± SD		5.24 ± 1.3	4.87 ± 0.98	t=1.58
	min- max		2.5 – 7.5	3.1 – 8	p=0.117
	low	1	1 (4)	0	X^2=1.9
	normal	86	12 (48)	74 (64.91)	p=0.17
	high	52	12 (48)	40 (35.09)	
HDL mmol/L	mean ± SD		0.93 ± 0.2	1.24 ± 0.3	t=5.18
	min- max		0.6 – 1.6	0.69 – 2.6	***p=0.000001
	low	29	18 (72)	11 (9.65)	X^2=47.8
	normal	109	7 (28)	103(90.35)	***p=0.0000
LDL mmol/L	mean ± SD		3.09 ±1.1	3.08 ± 1.3	t=0.04
	min- max		0.9 – 5.4	1.3 – 6.0	p=0.97
	low	91	16 (64)	75 (65.79)	Fisher´s exact
	normal	31	6 (24)	25 (21.93)	p=1.0
	high	17	3 (12)	14 (12.28)	
IL – 6	mean ± SD		10.85 ± 20.8	8.15 ± 16.9	Z=2.5
	min- max		2.04 – 101	1.39 – 101	*p=0.012
	median (IQR)		5.28 (4.11 – 6.9)	3.85 (2.75 – 6.07)	
	normal	116	20 (80)	96 (84.21)	p=0.565
	high	23	5 (20)	18 (15.79)	

t (Student t-test), X^2(Chi-square test)

*sig p<0.05, ***sig p<0.0001

Table 3 displays the results of univariate and multivariate logistic regression analyses used to determine the factors that have independent prognostic value in predicting the presence of MS in people living with HIV and receiving ART.

All variables that showed a significance level of at least 0.05 in the univariate analysis were entered into a model of multivariate regression analysis, including: hypertension (p=0.000), age (p=0.026), BMI (p=0.000), waist circumference (p=0.000), hip circumference (p=0.001), glycemia (p=0.001), triglycerides (p=0.000) and HDL (p=0.000).

The multivariate analysis identified the following independent significant prognostic factors for MS: BMI (p=0.019), waist circumference (p=0.001), glycemia (p=0.002), triglycerides (p=0.003) and (p=0.004); hypertensive patients had a 7.98 times higher risk of MS compared to non-hypertensive patients (7.98 CI 2.003-31.791); an increase in BMI of 1 kg/m^2 increased the risk of MS by 40.5% (1.405 CI 1.057-1.868); an increase in waist circumference by 1 cm increased the risk of MS by 14.4% (1.144 CI 1.061-1.235); a rise in serum glucose level by 1 mm/l increased the risk of MS by 50.1% (1.501 CI 1.200-4.468); an increase in triglycerides by 1 mm/l increased the risk of MS by 63.6% (1.636 CI 1.221-8.159); an increase in HDL by 1 mm/l decreased the risk of MS by 0.02% (0.002 CI 2.001-0.138).

Table 3. Binary logistic regression analysis to determine the factors that have an independent prognostic value for the onset of metabolic syndrome

	univariate				multivariate			
	p	**Exp (B)**	**95% CI for Exp (B)**		**p**	**Exp (B)**	**95% CI for Exp (B)**	
			Lower	**Upper**			**Lower**	**Upper**
gender	Ref gr. women							
men	0.33	2.391	0.413	13.843				
High TA	Ref gr. no				High TA ref gr. no			
yes	0.000	7.122	2.487	20.393	yes 0.003	7.980	2.003	31.791
Age	0.026	1.060	1.007	1.115				
BMI	0.000	1.325	1.173	1.498	0.019	1.405	1.057	1.868
Waist circumference	0.000	1.122	1.067	1.179	0.001	1.144	1.061	1.235
Hip circumference	0.001	1.106	1.045	1.171				
glucose	0.001	2.682	1.520	4.733	0.002	1.501	1.200	4.468
triglycerides	0.000	3.95	2.36	6.611	0.003	1.636	1.221	8.159
HDL	0.000	0.001	0.001	0.024	0.004	0.002	0.001	0.138
cholesterol	0.119	1.383	0.920	2.080				
LDL	0.967	1.010	0.625	1.633				
CD4	0.314	1.786	0.578	5.519				
IL6	0.403	1.021	0.972	1.072				

Patients with and without MS did not differ significantly in terms of ART groups (p=0.45), ART >3 months (p=0.62) and frequency of HIV RNA >200 cop/ml (p=0.15).

Table 4. ART as risk factor for the onset of MS in people living with HIV infection and receiving ART for more than 3 months in RNM

variable		Metabolic syndrome			p-level
		n	yes N=25	no N=114	
ART groups n (%)	NRTI+NNRTI	108	18 (72)	90 (78.95)	X^2=0.57 p=0.45
	NRTI+INSTI	31	7 (28)	24 (21.05)	
ART>3 months	TDF/FTC+RPV	2	1 (4)	1 (0.88)	Fisher´s exact p=0.62
	TDF/FTC+EFV	55	7 (28)	48 (42.11)	
	TDF/FTC+RAL	8	2 (8)	6 (5.26)	
	TDF/FTC+DOR	52	10 (40)	42 (36.84)	
	ABC/3TC+DTG	12	2 (8)	10 (8.77)	
	TAF/FTC+BIC	9	3 (12)	6 (5.26)	
	ABC/3TC+RAL	1	0	1 (0.88)	
HIV RNA	< 200 copii/ml	135	23 (92)	112 (98.25)	p=0.15
	>200 copii/ml	4	2 (8)	2 (1.75)	

After 6 months of treatment, a statistically significant difference compared to baseline values was obtained for glycemia (p=0.000007), cholesterol (p=0.027) and LDL (p=0.034).

The average blood glycose levels after 6 months were 5.57 ± 0.9 mmol/L, against the initial values of 6.35 ± 1.1 mmol/L; the average difference of 0.78 mmol/l was statistically significant (p=0.000007).

Cholesterol levels significantly decreased from 5.24 ± 1.3 to 4.83 ± 0.99 mmol/L after 6 months; the mean difference of 0.41 mmol/l was statistically significant, for 0.027.

LDL significantly decreased from 3.09 ± 1.1 to 2.71 ± 0.6 after 6 months, the mean difference of 0.38 mmol/l was statistically significant (p=0.034).

Table 5. Characteristics of risk factors for MS in people living with HIV infection and receiving ART in RNM during a follow-up period of 6 months

Variable		Metabolic syndrome		p-level
		Baseline	After 6 months	
BMI	mean ± SD	28.82 ± 4.6	29.02 ± 4.5	t=0.77 p=0.45
	min- max	22.6 – 40.1	22.6 – 38	
waist circumference	mean ± SD	101.04 ± 12.4	100.28 ± 11.1	t=0.89 p=0.38
	min- max	84 – 130	83 – 124	
	normal n (%)	14 (56)	15 (60)	McNemar Chi=0.35 p=0.56
	high n (%)	11 (44)	10 (40)	
Hip circumference	mean ± SD	105.84 ± 9.1	105.44 ± 9.4	t=0.4 p=0.69
	min- max	90 – 120	92 – 128	
CD 4	mean ± SD	637.20 ± 304.4	703.96 ± 320.3	t=1.5 p=0.14
	min- max	90 – 1205	288 – 1485	
	low n (%)	5 (20)	2 (8)	McNemar Chi=1.33 p=0.25
	normal n (%)	20 (80)	23 (92)	
glucose	mean ± SD	6.35 ± 1.1	5.57 ± 0.9	t=5.7 ***p=0.000007
	min- max	4.8 – 9.3	3.7 – 8.2	
	low n (%)		1 (4)	McNemar Chi=0.5 p=0.48
	normal n (%)	17 (68)	18 (72)	
	high n (%)	8 (32)	6 (24)	
CRP	mean ± SD	3.84 ± 3.5	2.96 ± 2.9	

	min- max	1 – 12	1 – 14	Wilcoxon Matched Pairs Z=1.4 p=0.16
	median (IQR)	2 (1 – 6)	2 (1 – 3)	
	normal n (%)	24 (96)	24 (96)	
	high n (%)	1 (4)	1 (4)	
Triglycerides	mean ± SD	2.67 ± 1.1	2.61 ± 1.3	t=0.38 p=0.71
	min- max	1.03 – 5.24	0.87 – 5.7	
	normal n (%)	10 (40)	11 (44)	McNemar Chi=0.0 p=1.0
	high n (%)	15 (60)	14 (56)	
Cholesterol	mean ± SD	5.24 ± 1.3	4.83 ± 0.99	t=2.3 *p=0.027
	min- max	2.5 – 7.5	3 – 6.8	
	low n (%)	1 (4)		
	normal n (%)	12 (48)	18 (72)	McNemar Chi=3.2 p=0.07
	high n (%)	12 (48)	7 (28)	
HDL	mean ± SD	0.93 ± 0.2	0.91 ± 0.2	t=0.73 p=0.47
	min- max	0.6 – 1.6	0.7 – 1.6	
	low n (%)	18 (72)	5 (20)	McNemar Chi=0.25 p=0.62
	normal n (%)	7 (28)	20 (80)	
LDL	mean ± SD	3.09 ± 1.1	2.71 ± 0.6	t=2.25 *p=0.034
	min- max	0.9 – 5.4	1.6 – 4.4	
	low n (%)	16 (64)		Friedman ANOVA Chi Sqr. = 18.0 ***p=0.00002
	normal n (%)	6 (24)	24 (96)	
	high n (%)	3 (12)	1 (4)	
IL – 6	mean ± SD	6.87 ± 9.1	4.96 ± 3.8	Wilcoxon Matched Pairs Z=1.6 p=0.1
	min- max	1.5 – 49.52	0.5 – 16.6	
	median (IQR)	5.28(4.11 – 6.9)	3.75(2.56 – 7.03)	
	normal n (%)	20 (80)	19 (76)	McNemar Chi=0.0 p=1.0
	high n (%)	5 (20)	6 (24)	

t(Student t-test for dependent samples)

*sig p<0.05, ***sig p<0.0001

Statistical analysis

SPSS statistical software (ver. 23.0; IBM, SPSS, USA) was used for statistical analysis. Kolmogorov-Smirnov and Shapiro Wilk's tests were used to test the normality of data distribution.

Categorical (attributive) variables are shown with absolute and relative numbers. Numerical (quantitative) variables are shown with mean, standard deviation, minimum and maximum values, median value and interquartile range. The Fisher exact test or the Chi-square test was used to compare the two groups in terms of categorical (attributive) variables; to compare numerical (quantitative) variables, depending on the data distribution, non-parametric and parametric tests for independent samples (Student t-test for independent samples and Mann-Whitney test) were used.

Logistic regression analysis with determination of odds ratio (OR) and 95% CI was used to determine the factors associated with metabolic syndrome.

Statistical significance was defined at $p<0.05$.

Discussion

According to the data analyzed in our study, the prevalence of MS was 17.96% based on the criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) 2005 in people living with HIV and who were on ART for more than 3 months. In a systematic analysis of studies from developing countries from regions in Africa, South America, and Asia, the prevalence of MS ranged from 8.4% to 47%, with Africa 30.5%, Asia 21.5%, and South America 21.4% [14].

The results for the prevalence of MS in people living with HIV in the Republic of North Macedonia were similar with data from a meta-analysis of 65 studies from five continents. In a study by Ayodele from 2012, the prevalence of MS in people living with HIV in Nigeria was 17.2%; in a study by Alencastro from 2012, the prevalence of MS in Brazil was 17.2%, while in a study by Biron conducted in France in 2012, the prevalence was 18.2% [7]. In the same meta-analysis using the criteria of the NCEP ATP III 2001, a similar prevalence was shown in two studies in Italy by Maloberti from 2013 and Schiliaci from 2008 of 17.6% and 17.9%, respectively [7].

Certain sociodemographic risk factors were found to be statistically significant for the development of MS in people living with HIV and receiving ART in the Republic of North Macedonia. HIV-infected patients with MS were significantly older and had a higher body mass index, implying that aging and weight gain significantly influenced on the development of MS in people living with HIV and receiving ART, with extended life expectancy.

At the same time, no significant difference was observed regarding smoking status and alcohol use in the groups with and without MS. The results of the multivariate analysis showed that a 1 kg/m^2 increase in BMI increased the risk of metabolic syndrome by 40.5% (1.405 CI 1.057-1.868). An association of the same risk factors identified in our study in the development of MS has already been shown in a study conducted in Kenya, where a prevalence of MS in HIV- infected individuals on ART was 16.9% [6].

The aging increases the risk of MS because it reduces the ability of beta cells of the pancreas to secrete insulin, and increases the risk of diabetes. Additionally, it reduces the stability of vascular membranes, thus increasing the risk of hypertension. Also, aging increases the risk of lipid abnormalities, dysfunctional adipose tissue, and consequently, the risk of cardiovascular diseases.[15]

The criteria used in defining MS have already been proven to be risk factors for the development of MS. Certain criteria that showed a higher frequency, such as hypertension which was present in 80% of patients with MS, elevated triglycerides in 60% of patients, and decreased HDL cholesterol levels in 72%, indicated the need for regular monitoring of people living with HIV who are receiving ART in North Macedonia. Detection of individuals at risk and timely treatment of these risk factors are crucial in preventing the onset of MS.

Treatment of patients with two NRTIs and one NNRTI, as well as a combination of ART of two NRTIs with one INSTI did not show a significant difference in the group with and without MS. Furthermore, no significant difference was obtained in the presence of MS in individuals receiving combined ART that included one of the following NNRTI drugs: efavirenz, doravirin, rilpivirin, INSTI: dolutegravir, raltegravir and bictegravir.

Previous studies have shown that there is an association of MS with ART treatment that includes a protease inhibitor (PI). In our study, none of the included patients were treated with PI, which could be the reason for the lack of association of ART with MS. In a study of 850 HIV infected patients receiving ART in the United States, the prevalence of MS was 26%, while in a Ugandan study of 250 HIV-infected patients receiving an ART regimen with NNRTIs, the prevalence of MS was 58% [6].

In these studies, patients were significantly older and had elevated BMI values as a risk factor for the occurrence of MS, which was also the case in our study. The discrepancy in prevalence rate is likely due to the diagnostic criteria used to define MS in the Ugandan study, as well as the ART regimen given to patients in our study. Patients in our study were not on PI contrary to the cohort in the USA study where 31% of patients were on an ART regimen that included PI [6].

The use of newer ART regimens, including second generation INSTIs such as DTG and BIC that are considered to have a better safety profile for MS onset in our patients could also account for the absence of an association of ART with MS onset. A retrospective observational study of the efficacy, safety and

tolerability of one of the newer INSTIs - BIC showed that lipid profile, body weight, BMI and liver function were not affected when changing the ART regimen to a regimen including BIC/FTC/TAF and not registered development of metabolic syndrome or weight gain [16].

In a retrospective study, weight gain was monitored in patients who switched their ART regimen from EFV/TDF/FTC to a regimen that included INSTIs or PIs. These patients were compared to patients who remained on the EFV/TDF/FTC regimen over an 18-month-period. Patients who switched to the INST regimen had a 2.9 kg increase in TT compared to those who remained on the efavirenz regimen. This is supported by another study involving 460 patients who had achieved viral suppression and switched to a regimen including DTG, and showed an increase in BMI of 0.8 kg/m^2 per year during the year of initiation of dolutegravir therapy, rising to 1.2 kg/m^2 per year thereafter [16].

The effects of HIV infection and ART regimens characterized by central lipohypertrophy (increased visceral fat deposition) and lipoatrophy (loss of peripheral fat) are the reason why change in waist circumference is a better marker of MS in people with HIV infection than BMI, which does not include the abnormality of fat distribution.

The accumulation of visceral adipose tissue is one of the main causes of increased inflammation-associated body composition. Adipocytes consequently express IL-6 and tumor necrosis factor alpha which through the portal circulation of the liver reach Kupffer cells and stimulate them to produce C-reactive protein and other inflammatory markers [8].

In our study, no significant difference was shown in terms of viral suppression expressed through the level of HIV RNA in serum, immune reconstitution through the number of CD4 cell/ml and C-reactive protein in the group with HIV infection and MS compared to the group without MS. However, there was a significant difference regarding the frequency of IL-6 (p=0.012).

One possible reason for this could be the fact that patients in the study had been on ART for more than 3 months and most of them achieved viral suppression and immune reconstitution. Untreated HIV infection was associated with increased levels of interleukin 6, a pro-inflammatory cytokine and stimulator of C-reactive protein production.

High levels of interleukin 6 were a strong predictor of cardiovascular diseases and consequently higher mortality in people with HIV infection not treated with ART. Whether this immunomodulatory and proinflammatory effect is a consequence of HIV viremia, the extent of CD4 cell decline, or other processes remains unclear [11].

Conclusion

In people living with HIV infection in the Republic of North Macedonia who have been receiving ART for more than 3 months the prevalence rate of MS is 17.96%.

From the defined criteria for MS in patients with HIV infection who are on ART in North Macedonia, hypertension, hypertriglyceridemia and reduced HDL cholesterol are most prevalent. Therefore, these parameters should be regularly monitored in order to enable early diagnosis and treatment of associated risk factors and to prevent the onset of MS.

Aging and increasing BMI are significant risk factors for the development of MS in people living with HIV who are receiving ART.

The use of newer generations of antiretroviral drugs in combined ART reduces the risk of MS in people living with HIV and who are on ART in North Macedonia.

The efficacy of ART enables viral suppression and immune reconstitution, which reduces the chronic inflammatory process caused by the HIV virus. High levels of interleukin 6 are a predictive factor for the onset of MS in HIV-infected patients who are receiving ART.

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