

Alexithymia Predicts Carotid Atherosclerosis, Vascular Events, and All-Cause Mortality in Human Immunodeficiency Virus-Infected Patients: An Italian Multisite Prospective Cohort Study

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Background. Psychological factors (PFs) are known predictors of cardiovascular disease (CVD) in many clinical settings, but data are lacking for human immunodeficiency virus (HIV) infection. We carried out a prospective study to evaluate (1) psychological predictors of preclinical and clinical vascular disease and (2) all-cause mortality (ACM) in HIV patients.

Methods. We conducted a cross-sectional analysis of baseline data to evaluate the predictors of carotid plaques (CPs) and a prospective analysis to explore predictors of vascular events (VEs) and ACM over 10 years. Human immunodeficiency virus patients monitored at the Infectious Disease Units of 6 Italian regions were consecutively enrolled. Traditional CVD risk factors, PFs (depressive symptoms, alexithymia, distress personality), and CPs were investigated. Vascular events and ACM after enrollment were censored at March 2018.

Results. A multicenter cohort of 712 HIV-positive patients (75.3% males, aged 46.1 ± 10.1 years) was recruited. One hundred seventy-five (31.6%) patients had CPs at baseline. At the cross-sectional analysis, alexithymia was independently associated with CPs (odds ratio, 4.93; 95% confidence interval [CI], 2.90–8.50; $P < .001$), after adjustment for sociodemographic, clinical, and psychological variables. After an average follow-up of 4.4 ± 2.4 years, 54 (7.6%) patients developed a VE, whereas 41 (5.68%) died. Age, current smoking, hypertension, and alexithymia (hazard ratio [HR], 3.66; 95% CI, 1.80–7.44; $P < .001$) were independent predictors of VE. Likewise, alexithymia was an independent predictor of ACM (HR, 3.93; 95% CI, 1.65–9.0; $P = .002$), regardless of other clinical predictors.

Conclusions. The present results validate our previous monocentric finding. Alexithymia may be an additional tool for the multifactorial assessment of cardiovascular risk in HIV.

Keywords. alexithymia; atherosclerosis; HIV; mortality; psychological factors.

Coronary artery disease is a major cause of morbidity and mortality for patients living with long-term human immunodeficiency virus (HIV) infection [1, 2]. Indeed, epidemiological studies, fully adjusting for numerous cardiovascular disease (CVD) risk factors and investigating validated cardiovascular (CV) events, demonstrate an increased risk of CV events in HIV versus non HIV-infected patients [3]. Between 1999 and 2013,

the proportion of mortality attributable to CVD among HIV-infected individuals aged 25 years or older in United States increased from 2.1% to 3.8% in women and from 1.9% to 4.9% in men [4]. After controlling for sex, race/ethnicity, borough of residence, and year, those with HIV had significantly higher CVD mortality than the general population in all age groups through age 65 [5]. There is a critical need to determine efficacious CV risk reduction interventions in HIV-infected patients. So far, preventive strategies have focused on managing of traditional CVD risk factors (such as smoking, lipodystrophy, diabetes, hypertension, and dyslipidemia), effect of highly active antiretroviral therapy (HAART) on CVD risk and immune activation [6]. However, in the field of CV risk prevention on the general and clinical population, epidemiological studies conducted in the last decade also generally demonstrate strong dose-response relationships between an increasing number of psychological risk factors and CVD [7, 8]. This has been poorly considered

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in the HIV-positive population until now. Psychological factors may be related to atherosclerosis and other vascular events (VEs) through their association with behavioral risk factors [9]. They may also directly affect biological processes by multiple pathways, such as inflammation [10], CV reactivity [11], endothelial dysfunction [12], platelet activation [13], and autonomic dysfunction [14], whereby psychological factors may play both a primary and a secondary pathogenic role, as shown by etiological and prognostic studies [7, 15]. Along these lines, we performed a single-center cohort study to evaluate the role of psychological factors, including alexithymia, distress personality (Type D), and depressive symptoms, in parallel with several traditional predictors of increased carotid intima-media thickness (c-IMT), carotid plaques (CPs), and ensuing VEs in 200 HIV-infected patients. We were able to show that alexithymia, a compromise of affective regulation and emotional cognitive processing, can act as an independent predictor of CPs and VEs in the HIV population [16]. In this study, we present the results of the multicentric validation of our results.

METHODS

Study Design

The study included (1) a cross-sectional analysis of the baseline data to evaluate the predictors of CPs and (2) a prospective cohort analysis to explore the determinants of VE and all-cause mortality (ACM) during the 10-year observation period. For this prospective cohort study, we recruited HIV-infected patients from provincial referral hospitals in several Italian regions including northern Italy, central Italy, southern Italy, and the major islands (Sicily and Sardinia). Patients were enrolled from the following: Infectious Disease Units of Pescara General Hospital (Abruzzo Region) since December 2007; Department of Medical, Surgical and Experimental Sciences, University of Sassari (Sardinia Region) from October 2014; Department of Clinical and Experimental Medicine, Garibaldi Nesima Hospital, University of Catania (Sicily Region) from November 2014; Department of Medicine, Santa Maria Hospital, Perugia (Umbria Region) from June 2015; Santa Maria Annunziata Hospital, Florence (Tuscany Region) from June 2015; and University of Bari (Puglia Region) since July 2016. All recruited patients were followed-up until March 20, 2018. Patients were reassessed every 6 months.

Data Collection

This study involved HIV-1-infected patients aged 18 and over and followed in the context of the CISAI study group (Italian Coordination for Research into Allergy and HIV Infection). Data were collected in real time by clinicians. The clinicians of each center had their own data collection database, which was sent to the referring center at each follow-up time point. The database underwent periodic quality control, including

comorbidity data. All patients were included in the cohort after receiving oral information and giving written consent. All patient information was entered into a database using anonymous, coded identification numbers. The present study only included Infectious Diseases Units already collecting psychological and neurocognitive parameters as a part of good clinical practice according to the Italian guidelines for the use of antiretroviral agents and the diagnostic-clinical management of the HIV-1 infection of the Society of Infectious and Tropical Diseases and of the Technical Health Committee, Italian Ministry of Health [17]. Indeed, at participating centers, psychological screening was performed in the context of the usual clinical practice. Furthermore, each participating center was authorized to confer anonymized data for retrospective research purposes by local authorities. Because the present study was set up as a multicentric collection of existing clinical data, and no additional experimental intervention was required for participants, the preliminary opinion of local ethics committees was not required in accordance to local ethical rules. This study was performed in accordance with the principles of the Declaration of Helsinki and current Italian legislation relating to biomedical research. Inclusion criteria were as follows: treated or untreated confirmed chronic HIV infection; age ≥ 18 years; any CD4 T-cell counts and HIV viremia; absence of acute opportunistic infections, malignancy, or pregnancy at the time of enrollment and subsequent study procedures; sufficient knowledge of the Italian language to undergo psychological profiling; and willingness and ability to provide written informed consent. All consecutive HIV-infected patients aged 18 years or more, attending the Outpatient Clinics of the unit of infectious diseases mentioned above, were offered participation at their first access.

Demographic, Clinical, and Viro-Immunological Characterization of the Sample

At the baseline visit, each patient agreeing to participate underwent an in-depth assessment, covering sociodemographic, anthropometric, and clinical characteristics (Table 1). Data on participants' lifestyle behavior information were obtained through an ad hoc structured self-report questionnaire, following international recommendations [18–20]. The centers participating in the study routinely evaluated the patient's adherence to antiretroviral therapy at each visit. The method to define the level of adherence adopted spontaneously by all participating centers was to ask patients whether they had taken regular therapy (from the previous visit) based on the prescription. The level of adherence was defined as the division of the pill number that the patient actually used by the pill number that the patient must have used, multiplied by 100. An adherent patient was defined as one who takes $>95\%$ of the prescribed doses. Patients with a reported intake of less than 95% of the doses were classified as suboptimal adherents.

Table 1. Overall Characteristics of the Sample at Baseline

Variables	Overall Sample (n = 712)
Sociodemographic Characteristics	
Male gender, %	75.3
Mean age in years (SD)	46.1 (10.1)
Married, %	33.8
Low educational attainment (<13 years), %	43.3
Stable employed, %	67.3
Race/Ethnicity	
White, %	97
Black, %	1.4
Hispanic or Latino, %	1.6
HIV Transmission Risk Factor	
IDU, %	25.8
MSM, %	33.6
Heterosexual, %	40.6
Lifestyle Factors	
Smoke, %	51.7
Alcohol abuse, %	11.2
Physical activity, %	29.9
Cardiovascular Risk Factors	
Mean BMI (SD)	24.2 (4)
Mean total cholesterol, mg/dL (SD)	192 (51.9)
Mean HDL cholesterol, mg/dL (SD)	42.7 (13.6)
Mean LDL cholesterol, mg/dL (SD)	117.6 (38.6)
Hypertension, %	20.4
Fasting glucose, mg/dL (SD)	89.6 (21.5)
Diabetes, %	10.4
Mean carotid intima-media thickness in centimeters (SD)	0.07 (0.04)
Carotid atherosclerotic plaques, %	31
Previous vascular events (overall), %	2.6
Previous AMI, angina, or PCI, %	31.6
Previous stroke or TIA, %	36.8
Previous cardiac syncope, %	10.6
Previous intestinal infarction or renal infarction, %	21
Positive CVD family history ^a , %	44
FRS 10-year general CVD risk, mean % of risk (SD)	7.7 (8.1)
FRS% of risk >20, %	11.3
FRS% of risk 20–10, %	21.2
FRS% of risk <10, %	67.5
HIV-Related Variables	
AIDS diagnosis, %	32.4
Nadir LyCD4, cell/mm ³ (SD)	244 (189)
Baseline LyCD4, cell/mm ³ (SD)	639.8 (360.3)
Baseline LyCD4 cell count <200 cells/mm ³ , %	9.3%
Baseline HIV-RNA copies/mL (SD)	13 381.1 (77 065.3)
HIV-RNA <50 copies/mL, %	77.9
Mean duration of HIV infection in years (SD)	13.1 (8.1)
Treated with HAART, %	91.4
Mean duration of HAART in months (SD)	103.2 (84.5)
Lipodystrophy, %	25.8
Suboptimal adherence to HAART, %	7.5
Other Treatment	
Antihypertensive medication	18.3
Antiplatelet/anticoagulant medication	5.8
Psychiatric medication	16
Comorbidities	
HCV coinfection, %	25.2

Table 1. Continued

Variables	Overall Sample (n = 712)
Neoplastic disease, %	10.7
Psychological Factors	
Depressive symptoms, %	22
Depressive symptom (BDI-II) score (SD)	11 (10.3)
Alexithymia, %	36.0
Alexithymia (TAS-20) score (SD)	45.9 (13.2)
Distress personality (Type D), % ^a	39

Abbreviations: AIDS, acquired immune deficiency syndrome; Alexithymia, Toronto Alexithymia Scale (TAS-20) >50; AMI, acute myocardial infarction; BDI-II, Beck Depression Inventory-II; BMI, body mass index; CVD, cardiovascular disease; FRS, Framingham risk score; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; IDU, injection drug user; LDL, low-density lipoprotein; LyCD4, CD4 lymphocyte; MSM, men who have sex with men; PCI, percutaneous coronary intervention; RNA, ribonucleic acid; SD, standard deviation; TIA, transient ischemic attack;

^aMissing values ≥10%.

Definition of the Main Outcomes

The main outcomes of our investigation were as follows: (1) presence of CPs at baseline; (2) VEs during follow-up (every 6 months), including acute myocardial infarction (AMI), angina or percutaneous coronary intervention (PCI), stroke or transient ischemic attack (TIA), cardiac syncope, organ infarctions (intestinal infarction or renal infarction), and peripheral artery disease (PAD); (3) ACM including acquired immune deficiency syndrome (AIDS) malignancy (diffuse centroblastic lymphoma, plasmoblastic lymphoma), CVD (myocardial infarct, stroke, pulmonary edema, other organ infarct), non-AIDS malignancy (prostate cancer, malignant melanoma, lung cancer, Hodgkin lymphoma, gastric cancer, pancreas cancer), non-AIDS infection (sepsis, infective endocarditis, pneumonia), liver disease, pulmonary disease (chronic obstructive pulmonary disease, pulmonary hypertension), violent or accidental death (suicide, physical assault, trauma). All ultrasonographic scannings of carotid arteries (short and long axis) were performed by certified operators. Vascular events were actively searched in the cohort. They were positively assessed at each follow-up visit by the assisting physicians and recorded in the study dataset when appropriate, after review of clinical, laboratory, and imaging data supporting diagnoses of each VE. Records of all patients dying during follow-up were also reviewed before inclusion in the dataset.

Definitions and Measures of the Psychological Constructs

Three psychological parameters—depressive symptoms, distress personality [Type D], and alexithymia—were evaluated for their relevance in the CV risk area [7, 16, 21–23]. Depressive symptoms were evaluated with Beck Depression Inventory-II (BDI-II) [24] using a specific cutoff for the HIV-infected population (BDI-II score ≥17) [25]. Type D is a relatively new construct characterized by 2 global personality

traits: negative affectivity (NA) and social inhibition (SI) [26]. Type D was evaluated with Italian-validated [27] DS-14 (NA score ≥ 9 ; SI score ≥ 9 , as opposed to the original DS-14 cutoff of 10). Alexithymia refers to the psychological dysfunctional trait of having no words to express emotions or feelings [28]. It is a multidimensional construct comprising emotional and cognitive components: difficulties in identifying and describing feelings as well as in differentiating somatic sensations and feelings, lack of fantasy and imagination, and an externally oriented cognitive style [28]. It is interesting to note that the relevance of alexithymia has grown exponentially in the last decades; it is currently considered a relevant concept for a range of psychological and physical disorders [28]. We used the Italian version of the Toronto Alexithymia Scale-20 item (TAS-20), which is universally used for the alexithymia construct worldwide [29]. The TAS-20 cutoff point >50 (including borderline alexithymia + high alexithymia), a threshold previously used in studies on large populations [21, 22], was chosen because it proved to be more sensitive in predicting CV risk in the general and clinical population [16, 21, 22].

Statistical Analysis

Cross-Sectional Analysis of Baseline Data

Multivariable logistic regression analyses were used to evaluate potential independent predictors of the presence of CPs, treated as a dichotomic variable. We defined the regression model including a priori several potential confounders (age, gender, body mass index [BMI], smoking, hypertension, diabetes, one among total cholesterol, physical activity, alcohol/drug abuse, educational level, and infection duration), because of their known association with CPs, and including other eventually significant variables, which were selected using a stepwise forward process (including in model fitting all variables that were significant at a 0.10 level in univariate analyses). Each covariate was tested in its original form or transformed if needed. In addition, each included variable was tested for multicollinearity, for potential interaction and/or quadratic/cubic terms. We found only total and low-density lipoprotein (LDL) cholesterol to be collinear and chose to include total cholesterol. For continuous covariates for which a defined threshold has been indicated in the literature (ie, TAS-20 score >50), we tested the inclusion of both the continuous and categorical form, and we selected the one that was included in the model with highest pseudo or adjusted R-squared values. All variables that were not included into the final models were not significant. In addition, we tried to limit, as much as possible, the number of covariates included in the final model to avoid overfitting; among the nonsignificant variables, inside the final model, we left those that were associated with the highest increase in model pseudo or adjusted R-squared, or those that changed the significant coefficients by more than 10%. The results of the logistic analysis are presented as odds ratio (OR) and 95% confidence limits.

Survival Analysis of Follow-up Data

Cox proportional hazards analysis was used to calculate the adjusted relative hazards of VEs and ACM by each variable. Stochastic level of entry into the model was set at 0.10, and interaction terms were explored for all variables in the final model. A minimum events-to-variable ratio of 10 was maintained in multivariate modeling to avoid overfitting, and Schoenfeld's test was performed to check the validity of proportional hazards assumption. Kaplan-Meier survival analysis was used to examine the association between a TAS-20 score >50 and VEs or ACM. Statistical significance was defined as a 2-sided *P* value $<.05$ for all analyses, which were performed using STATA 10.1 (StataCorp, College Station, TX).

RESULTS

Study Sample

The initial cohort screened for eligibility to participate in the study consisted of 743 patients. Twelve HIV-infected patients visiting occasionally were not offered participation. Nineteen patients were excluded due to linguistic barriers. Nineteen VEs were not computed before the start of the study. The final sample was 712 patients, all of whom gave informed consent to participate. Of them, 553 (77.7%) attended CPs evaluation, 660 (92.7%) had a psychological assessment, and 508 (71.3%) had both procedures and could thus be included in the multivariate analyses. The clinical, behavioral, and sociodemographic characteristics of the final sample ($n = 712$) are described in [Table 1](#). The mean age was 46.1 years, 75% were males, the mean BMI was 24.2, 20% had hypertension, 10% had diabetes, 51% were active smokers, and the mean 10-year Framingham risk score was 7.7%. Seventy-seven percent of patients were virologically suppressed and 91.4% were treated with HAART. Additional information is detailed in the [Supplemental Material](#).

Predictors of Carotid Plaques: Cross-Sectional Analysis

One hundred seventy patients (31.6%) were found to have at least 1 vascular carotid lesion that met the primary (≥ 1.5 mm) definition of CPs. As shown in [Table 2](#), at univariate analyses, presence of CPs was significantly associated with older age, low education, stable employment, smoking, HIV transmission risk factor (injection drug user [IDU]), total cholesterol and LDL, hypertension, diabetes, Framingham risk score, AIDS diagnosis, nadir CD4 T-cell counts, duration of HIV infection, treatment with HAART and its duration, lipodystrophy, depressive symptoms, and alexithymia. At multivariate analyses, only male gender, increasing age, total cholesterol, hypertension, years lived with HIV, and alexithymia remained significantly associated with CPs ([Table 2](#)). In particular, subjects with a TAS-20 score >50 (presence of alexithymia) consistently showed an OR of 4.9 (95% confidence interval [CI], 2.9–8.5; $P < .001$) of having CPs.

Table 2. Univariate and Multivariate Analyses Evaluating the Potential Predictors of Each Recorded Outcome

Variables	Carotid Plaques at Baseline			Vascular Events			Overall Mortality					
	(n = 175)	P ^a	OR (95% CI)	P ^b	(n = 54)	P ^c	HR (95% CI)	P ^d	(n = 41)	P ^e	HR (95% CI)	P ^f
Sociodemographic Characteristics												
Male gender	80.5%	.3	1.84 (.99–3.42)	.05	90.7%	.006	2.31 (.85–6.24)	.09	87.8%	.06	–	–
Mean age in years (SD) ^d	51.8 (9.5)	<.001	1.08 (1.05–1.12)	<.001	53.8 (9.9)	<.001	1.07 (1.02–1.1)	.002	49.1 (10.6)	.04	1.05 (1–1.08)	.023
Married	41.6%	.08	–	–	44%	.1	–	–	51.1%	.015	–	–
Low educational attainment (<13 years)	50.4%	.006	–	–	44.9%	.8	–	–	61.5	.017	–	–
Stable employed	58.8%	.004	0.83 (.47–1.84)	.5	50.9%	.027	–	–	43.2%	.005	–	–
Race/Ethnicity		.412	–	–	–	.9	–	–	–	.739	–	–
White	32.1%		–	–	96.3%		–	–	95%		–	–
Black	12.5%		–	–	1.85%		–	–	2.5%		–	–
Hispanic or Latino	22.2%		–	–	1.85%		–	–	2.5%		–	–
HIV transmission risk factor		.038	1.19 (0.85–1.66)	.3		.031	.92 (.63–1.33)	.6		.061	–	–
IDU	26.6%		–	–	37.74%		–	–	39%		–	–
MSM	28.4%		–	–	18.86%		–	–	19.5%		–	–
Heterosexual	45%		–	–	43.4%		–	–	41.5%		–	–
Lifestyle Factors												
Smoke	58.1%	.008	1.64 (0.97–2.77)	.06	69.8%	.001	2.02 (1.01–4.04)	.044	70.7%	.03	–	–
Alcohol abuse	8.8%	.3	–	–	15.7%	.2	–	–	40.5%	<.001	2.52 (1.09–5.81)	.03
Physical activity	25.9%	.2	–	–	24.5%	.3	–	–	14.6%	.028	–	–
Cardiovascular Risk Factors												
Mean BMI (SD) ^e	24.1 (3.9)	.6	–	–	25.4 (4.5)	.02	1.01 (0.94–1.09)	.6	25.6 (4.7)	.03	–	–
Mean total cholesterol, mg/dL (SD) ^f	199 (55.5)	.03	1.05 (1–1.01)	.042	195.6 (54.4)	.5	–	–	165 (52.5)	.001	–	–
Mean HDL, mg/dL (SD) ^e	41.3 (13.6)	.13	–	–	40.4 (11.7)	.046	–	–	32.5 (13.2)	<.001	–	–
Mean LDL, mg/dL (SD)	125.2 (46.9)	.004	–	–	118.2 (43.4)	.9	–	–	103.04 (33.5)	.06	–	–
Hypertension, %	32%	<.001	1.75 (1–3.06)	.045	51.8%	<.001	2.23 (1.15–4.32)	.017	29.3%	.2	–	–
Fasting glucose, mg/dL (SD)	95.7 (20.1)	.0007	–	–	99.4 (28.1)	.0009	–	–	103.8 (24.9)	.0001	–	–
Diabetes	16.4%	.003	1.04 (.48–2.26)	.9	25%	<.001	0.77 (0.35–1.68)	.4	34.2%	<.001	1.84 (.88–3.82)	.09
Mean carotid intima-media thickness in centimeters (SD)	0.10 (0.06)	<.001	–	–	0.08 (0.07)	.2	–	–	0.06 (0.02)	.11	–	–
Previous vascular event	4.57%	.23	–	–	0%	.2	–	–	4.8%	.35	–	–
Positive CVD family history	48%	.29	–	–	10%	.9	–	–	36.4%	.28	–	–
FRS 10-year general CVD, mean% of risk (SD) ^e	12.3 (9.3)	<.001	–	–	16.1 (10.7)	<.001	1.01 (.98–1)	.3	12.8 (10.1)	.005	–	–
HIV-Related Variables												
AIDS diagnosis	41.4%	.002	1.38 (0.83–2.29)	.2	49.1%	.002	1.31 (0.73–2.33)	.3	60%	<.001	1.96 (.98–3.93)	.05
Nadir LyCD4, cell/mm ³ (SD)	208 (192)	.006	–	–	227.5 (201.7)	.5	–	–	183 (146)	.05	–	–
Baseline LyCD4, cell/mm ³ (SD)	599.7 (331.9)	.95	–	–	600.1 (325.2)	.4	–	–	384.9 (245.6)	<.001	–	–
Baseline LyCD4 cell count <200 cells/mm ³	11.6%	.5	–	–	12%	.5	–	–	22.2%	.006	–	–
Baseline HIV-RNA copies/mL (SD)	13 601.4 (83 453.8)	.72	–	–	11 817 (40 281)	.8	–	–	9619.1 (34 667.3)	.78	–	–
HIV-RNA <50 copies/mL	77%	.93	–	–	6.6%	.1	–	–	66.6%	.12	–	–

Table 2. Continued

Variables	Carotid Plaques at Baseline			Vascular Events			Overall Mortality				
	(n = 175)	P ^a	OR (95% CI)	P ^b	(n = 54)	P ^c	HR (95% CI)	P ^c	(n = 41)	HR (95% CI)	P ^c
Duration of HIV infection in years (SD) ^d	15.8 (7.2)	<.001	1.05 (1.01–1.08)	.003	14.4 (7.7)	.2	–	–	13.6 (7.5)	–	–
Treated with HAART	94.3%	.02	–	–	90.6%	.8	–	–	83.7%	–	–
Mean duration of HAART in months (SD)	121 (82.3)	<.001	–	–	–	–	–	–	–	–	–
Lipodystrophy	40.1%	<.001	–	–	35.1%	.1	–	–	53.5%	–	<.001
Suboptimal adherence to HAART	10.6%	0.3	–	–	10.2%	.4	–	–	31.4%	–	<.001
Other Treatment											
Antihypertensive	47.5%	<.001	–	–	40.7%	<.001	–	–	29.3%	–	.06
Antiplatelet/anticoagulant	87%	<.001	–	–	38%	<.001	–	–	4.8%	–	.8
Psychiatric medication	38.5%	.1	–	–	26.5%	.027	–	–	31.8%	–	.004
Comorbidities											
HCV coinfection	28%	.2	–	–	27.8%	.6	–	–	43.9%	–	.005
Cancer	12.6%	.4	–	–	15.7%	.2	–	–	48.8%	–	<.001
Psychological Factors											
Depressive symptoms	27.7%	.017	.84 (0.46–1.55)	.5	44.2%	<.001	1.37 (0.72–2.58)	.3	40.5%	0.62 (0.28–1.4)	.2
Alexithymia	61.4%	<.001	4.93 (2.9–8.5)	<.001	74.5%	<.001	3.66 (1.8–7.44)	<.001	77.8%	3.93 (1.64–9)	.002
Distress personality (Type D) ^g	33.6%	.6	–	–	42.5%	.6	–	–	34.3%	–	.5

Abbreviations: aHR, adjusted hazards ratio; AIDS, acquired immune deficiency syndrome; Alexithymia, Toronto Alexithymia Scale (TAS-20) >50; aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; FRS, Framingham risk score; HAART, highly active antiretroviral therapy; HCV, high-density lipoprotein; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; IDU, injection drug user; LDL, low-density lipoprotein; LYCD4, CD4 lymphocyte; MSM, men who have sex with men; RNA, ribonucleic acid; SD, standard deviation.

^aχ² test for categorical variables; t test and Kruskal-Wallis test for normally distributed and nonnormally distributed continuous variables, respectively. In univariate analyses, all P values refer to the comparison between the subjects with and those without the selected outcome; eg, those with versus those without a baseline diagnosis of carotid plaques.

^bLogistic regression analysis including 450 observations (see text for covariates selection); Wald χ² = 96.8; Hosmer-Lemeshow goodness of fit P = .62; area under the receiver operating characteristic curve = 0.84.

^cCox proportional hazard analyses including 586 observations (vascular events) and 610 observations (overall mortality), respectively; see text for covariates selection.

NOTE: In all multivariate analyses: ^d = 1-year increase; ^e = 1-unit increase; ^f = 10-mg/dL increase; ^g = Missing values ≥ 10%.

Predictors of Vascular Events: Follow-up Survival Analysis

The mean follow-up of the 712 patients was 4.4 ± 2.4 years (for a total of 3133 person-years). Fifty-four patients (7.6%) experienced a VE during the follow-up: 23 (42.6%) experienced AMI, angina, or PCI; 15 (27.8%) experienced stroke or TIA; 3 experienced cardiac syncope (5.6%); 10 (18.5%) experienced intestinal infarction or renal infarction; and 3 (5.6%) experienced PAD. Eleven patients (7 males, 4 females, mean age 41 years) were lost-to-follow up. At univariate analyses, age, male gender, employment status, HIV transmission risk factor (IDU), smoking, BMI, lower high-density lipoprotein (HDL), hypertension, diabetes, Framingham risk score, AIDS diagnosis, depressive symptoms, and alexithymia were significantly associated with VEs. All other factors were not significantly associated with VEs. The incidence rate ratio of VEs was 5.8 (95% CI, 2.9–11.7) per 100 person-years among patients with alexithymia versus nonalexithymic. In the Cox proportional hazard model, age (hazard ratio [HR], 1.07; 95% CI, 1.02–1.10; $P = .002$), current smoking (HR, 2.02; 95% CI, 1.01–4.04; $P = .044$), hypertension (HR, 2.23; 95% CI, 1.15–4.32; $P = .017$), and alexithymia (HR, 3.66; 95% CI, 1.80–7.44; $P < .001$) were the only factors significantly associated with VEs (Table 2). The relationship between VEs and alexithymia is also apparent from the shape variation of the Kaplan-Meier estimates of time to event (Figure 1A).

Predictors of All-Cause Mortality: Follow-up Survival Analysis

The mean follow-up of the 712 patients was 4.3 ± 2.6 years (for a total of 3062 person-years). Forty-one patients (5.68%) died during the follow-up. Causes of death are detailed in the Supplemental Material. At univariate analyses, age, being married or unemployed, low education, smoking status, alcohol abuse, physical inactivity, BMI, total cholesterol and lower HDL, diabetes, AIDS diagnosis, Framingham risk score, low

CD4 count, nadir CD4 cell, lipodystrophy, suboptimal adherence to HAART, HCV coinfection, neoplastic disease, depressive symptoms, and alexithymia were significantly associated with mortality (Table 2). The overall incidence of ACM was 1.32 per 100 person-years. The incidence rate of ACM was 6.2 (95% CI, 2.7–15.7) per 100 person-years in patients with alexithymia. In the Cox proportional hazard model, age (HR, 1.05; 95% CI, 1.0–1.08; $P = .023$), alcohol abuse (HR, 2.52; 95% CI, 1.09–5.81; $P = .030$), AIDS diagnosis (HR, 1.96; 95% CI, 0.98–3.93; $P = .05$), suboptimal HAART adherence (HR, 2.62; 95% CI, 1.14–6.0; $P = .022$), and alexithymia (HR, 4.93; 95% CI, 1.64–9.00; $P = .002$) were the only factors significantly associated with ACM (Table 2). The relationship between ACM and alexithymia is also apparent from the shape variation of the Kaplan-Meier estimates of time to mortality (Figure 1B).

DISCUSSION

This is the first study to examine the prospective association between alexithymia and incident CV events and ACM among a multisite cohort of well characterized HIV-positive patients. In this setting, we established that alexithymia predicts CV events and ACM independently of demographic and other psychosocial, viro-immunological, and CV risk factors. Case-control studies on global large populations have documented that psychosocial factors are independent predictors for CV and cerebrovascular disease [8]. In the context of psychological factors, alexithymia is emerging as a potential CV risk indicator, with several studies suggesting a relationship between alexithymia, CVD, and CV mortality in the general population [21, 22]. Indeed, several CV risk factors, such as sympathetic overreactivity [30], inflammation [31], diabetes [32], obesity/metabolic syndrome [33, 34], and atherosclerosis [16, 21],

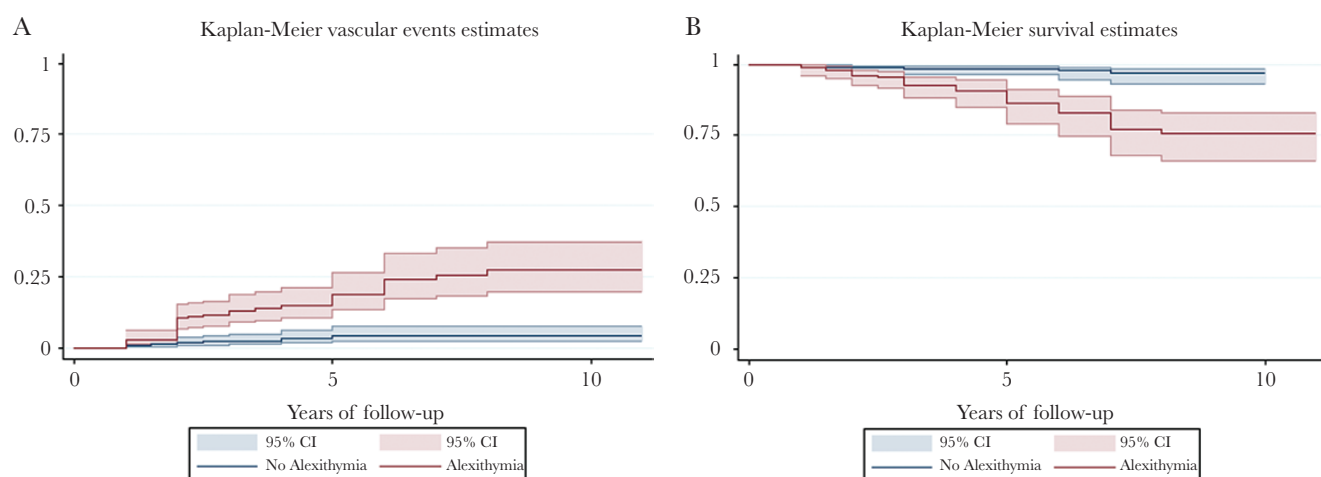


Figure 1. (A) Kaplan-Meier estimates of time to vascular events by alexithymia. (B) Kaplan-Meier estimates of time to all-cause mortality by alexithymia. CI, confidence interval.

Table 3. Overall Characteristics of the Sample at Baseline Stratified According to the Presence of Alexithymia

Variables	No Alexithymia N = 416 (64%)	Alexithymia N = 234 (36%)	P ^a
Sociodemographic Characteristics			
Male gender, %	75.7	75.2	.8
Mean age in years (SD)	45.3 (9.87)	47.8 (10)	.003
Married, %	33.3	34.9	.6
Low educational attainment (<13 years)	37	50.3	.003
Stable employed, %	72.2	53.1	<.001
Race/Ethnicity			
White, %	98.5	99.1	
Black, % ^b	–	–	
Hispanic or Latino, %	1.5	0.9	
HIV Transmission Risk Factor			
IDU, %	22.9	30.9	
MSM, %	36.7	27.8	
Heterosexual, %	40.4	41.3	
Lifestyle Factors			
Smoke, %	42.1	58.8	<.001
Alcohol abuse, %	7.7	17	<.001
Regular physical activity, %	37.5	20.2	<.001
Cardiovascular Risk Factors			
Mean BMI (SD)	23.9 (3.98)	24.5 (4.02)	.09
Mean total cholesterol, mg/dL (SD)	195 (48.25)	186 (50.38)	.036
Mean HDL cholesterol, mg/dL (SD)	44.9 (14.3)	42.1 (12.55)	.017
Mean LDL cholesterol, mg/dL (SD)	119.2 (37.26)	115.5 (40.55)	.2
Hypertension, %	21.9	24.4	.4
Fasting glucose, mg/dL (SD)	87.9 (19.82)	92.4 (23.87)	.013
Diabetes, %	6.7	13.9	.003
Mean carotid intima-media thickness in centimeters (SD)	.071 (.053)	.080 (.042)	.045
Carotid atherosclerotic plaques, %	20	55.6	<.001
Previous vascular events, %	2.4	2.5	.8
Positive CVD family history ^Ψ , %	51.8	37.2	.004
FRS 10-year general CVD risk, mean% (SD)	8.3 (9.37)	9.7 (8.74)	.09
FRS 10-year general CVD risk stratification			
FRS% of risk >20, %	11	12.9	
FRS% of risk 20–10, %	18.7	27.6	
FRS% of risk <10, %	70.3	59.5	
HIV-Related Variables			
AIDS diagnosis, %	33.3	33	.4
Nadir LyCD4, cell/mm ³ (SD)	247.5 (180.77)	236.7 (197.66)	.4
Baseline LyCD4 cell count <200 cells/mm ³ , %	7.4	13.3	.015
Baseline LyCD4, cell/mm ³ (SD)	670.4 (364.56)	592 (359.43)	.009
Baseline HIV-RNA copies/mL (SD)	11 779.4 (70 883.35)	18 210.6 (92 237.13)	.3
HIV-RNA <50 copies/mL, %	79.5	73.2	.07
Mean duration of HIV infection in years (SD)	12.8 (8.05)	13.6 (8.24)	.2
Treated with HAART, %	91.8	89.3	.3
Mean duration of HAART in months (SD)	103.8 (83.8)	106.4 (87.3)	.7
Lipodystrophy, %	22.4	32.5	.005
Suboptimal adherence to HAART, %	4.5	12.4	.001
Other Treatment			
Antihypertensive medication, %	18.7	20.5	.5
Antiplatelet/anticoagulant medication, %	5	7	.2
Psychiatric medication, %	12.2	22.4	.001
Comorbidities			
HCV coinfection, %	22.9	29.9	.049
Neoplastic disease, %	11	11.7	.7
Psychological Factors			
Depressive symptoms, %	10.4	44	<.001
Distress personality (Type D), % ^Ψ	29.3	55.5	<.001

Abbreviations: AIDS, acquired immune deficiency syndrome; Alexithymia, Toronto Alexithymia Scale (TAS-20) >50; BMI, body mass index; CVD, cardiovascular disease; FRS, Framingham risk score; HAART, highly active anti-retroviral therapy; HCV, high-density lipoprotein; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; IDU, injection drug user; LDL, low-density lipoprotein; LyCD4, CD4 lymphocyte; MSM, men who have sex with men; RNA, ribonucleic acid; SD, standard deviation.

^aχ² test for categorical variables; t test and Kruskal-Wallis test for normally distributed and nonnormally distributed continuous variables, respectively. All P values refer to the comparison between the subjects with and those without alexithymia.

^bTen HIV-positive South African patients did not compile the Toronto Alexithymia Scale due to difficulties in understanding the Italian language.

have been associated with a higher prevalence of alexithymia. A large prospective study on a cohort of over 2000 middle-aged persons showed that alexithymia is an independent predictor of both ACM and CV mortality [35, 36], with the risk of CV death increasing by 1.2% for each 1-point increase in Toronto Alexithymia Scale [22]. Consistently, in this multicentric cohort, alexithymic HIV patients had a higher prevalence of traditional CV risk factors at baseline compared with nonalexithymic HIV patients. Indeed, among alexithymics, we found a higher percentage of smokers and subjects with diabetes and less compliance to physical activity (Table 3). Nevertheless, when analyses were stratified by the presence of diabetes, alexithymia remained significantly and strongly associated with the presence of plaques, VEs, and ACM in nondiabetic subjects. Alexithymia also remained strongly associated with these 3 outcomes in the group of nonsmoking HIV alexithymic patients and in the group of alexithymic patients who performed regular physical activity.

To explain the strong association of alexithymia with CV outcomes and death in HIV, we can speculate that alexithymia may reflect a clustering of different risk factors (psychosocial and biological) that converges in a single patient with synergistic effects on health-related outcomes. Thus, the alexithymic component in people with HIV may be considered as a proxy for frailty, in that HIV-positive people with alexithymia tend to have a greater age, a higher percentage of smokers, and heavy alcohol drinkers and a higher percentage of individuals with diabetes, less compliance to physical activity, lower HDL, lower number of CD4 lymphocytes, a higher c-IMT, lower adherence to antiretroviral therapy, more frequent life-threatening habits that are more harmful for health, and marked psychopathological problems (Table 3).

It is worth noting that this is the first evaluation of the prevalence of alexithymia in an unselected multisite sample of HIV patients. We unraveled that HIV-infected patients have a higher prevalence of alexithymia compared with the general population, regardless of the TAS-20 threshold used. Indeed, the prevalence of severe alexithymia (TAS-20 >61) in our cohort was 15% against 9.9% of the general population [37], and the prevalence of both borderline and severe alexithymia (TAS-20 >50) was 36% versus 20.7% [21]. Moreover, among patients with carotid atherosclerosis, alexithymia was almost 3 times as frequent in HIV-positive subjects compared with a large seronegative population (23.8% vs 61.3%) [21]. The higher prevalence of alexithymia in people with HIV may suggest an effect of HIV on the central nervous system (CNS). Indeed, the alexithymic tract was associated at baseline with indicators of disease severity such as low CD4 T-cell counts (<200 cell/mm). The neurologic sequelae of HIV infection arise as a direct result of viral replication in the CNS as well as from the subsequent neuroinflammatory processes. Alexithymia, which is often associated with HIV, may reflect

effects of the virus on brain areas such as the prefrontal and anterior cingulate cortex (ACC) [38]. In fact, it has previously been documented that lower CD4 is associated HIV-related ACC atrophy and decreased ability to recognize emotions [39]. Preliminary data on non-HIV people have documented in the alexithymics a decreased neuronal activity mediated by increased GABA concentration in ACC [40]. A remarkable property of this ACC tissue is that it has more extensive projections than any other cortical region to autonomic regulatory structures, consistent with stimulation studies showing effects of cingulate electrical stimulation on virtually all autonomic and many endocrine functions [41]. These mechanisms may mediate the role of alexithymia on central regulation of CV functioning. Moreover, in our population, the increased risk of alexithymics for adverse health outcomes can be mediated by higher likelihood of alexithymics to harmful lifestyle habits (in an attempt to compensate for the reduced capacity for affective self-regulation with external regulators) and by a suboptimal adherence to HAART. This aspect is likely to be the basis of a looping process in which all patients with alexithymic disease not exposing themselves to therapeutic HAART concentrations are more at risk of having neurocognitive sequelae with the further worsening of the alexithymic condition.

CONCLUSIONS

Some limitations should also be acknowledged. First, alexithymia was measured at only 1 time point, and changes in the TAS-20 score could not be captured on the total sample. However, data collected on a fraction ($n = 105$, 16.5%) of patients in our sample, who were retested for psychological traits after an average of 18 months since their first evaluation, revealed that alexithymic scores were only minimally modified (data not shown), indicating a remarkable stability of this psychological phenotype over time, in line with the main prospective studies on alexithymia [42, 43]. Second, information about abdominal obesity, diet, and previous smoking, variables potentially associated with CV outcomes, is missing. The major strengths of our study are the accurate consecutive multisite enrollment of the study sample, the contextual evaluation of both psychological traits and CPs, psychological traits being evaluated by a certified investigator, and the active follow-up for VEs and ACM, which allowed limiting data censoring to a minimum in the final Cox's multivariate models. This result requires confirmation from studies with larger samples and longer follow-up. Indeed, further research is strongly justified: our results, if confirmed, can open the way for a new wave of preventive strategies targeting alexithymia for the control of CV disorders in the HIV population.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader,

the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. F. Va., F. Sa., and G. P. supervised the study. F. Va. and G. P. designed the study. F. Va., F. So., P. D. S., E. T., G. D. S., P. M., G. N., B. Z., V. L., F. V., C. B., E. P., and A. S. enrolled patients and collected data at the study sites. F. Va., F. So., P. D. S., and E. P. created and managed the database. F. Va., G. P., L. M., M. E. F., F. So., and F. Sa. analyzed and/or interpreted the data. L. M., M. E. F., G. P., and F. Va. acted as supervisor for data analysis and/or interpretation. F. Va., G. P., and F. Sa. drafted the initial manuscript. F. Va., G. P., F. Sa., G. M., G. D. S., P. M., L. M., M. E. F., and P. B. reviewed and/or revised the manuscript. F. Va., F. So., G. M., G. D. S., P. M., G. N., F. Vi., P. D. S., E. T., E. P., A. S., B. Z., V. L., C. B., M. E. F., P. B., F. So., L. M., and G. P. approved the final manuscript.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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Supplemental materials

Methods

Following the criteria of the Italian National Institute of Health we have considered as “smokers” individuals who smoke regularly every day even a single cigarette, or stopped less than 12 months ago [1]. Sedentary behavior was defined according to the 2008 Physical Activity Guidelines for the Americans as no regular physical activity (< 1 time/week), or regular physical activity as at least 150 minutes per week of moderate-intensity aerobic activity or 75 minutes per week of vigorous aerobic activity, or a combination of both, preferably spread throughout the week [2]. According to Italian National Institute of Health we considered "heavy drinking" (alcohol abuse), a consumption of 2 alcoholic units per day for men and 1 alcoholic unit per day for women [3]. The alcoholic unit corresponds to 12 grams of ethanol, contained in a can of beer (330 ml), a glass of wine (125 ml) or a small glass of liqueur (40 ml).

Results- Study sample

Between patients with and without ultrasonographic examination, no significant differences were found: mean age was 45.9 ± 9.9 y and 46.5 ± 10.6 y ($p=0.5$); smoke habit were 49.7% and 42% ($p=0.07$); mean BMI was 24.2 ± 4.1 and 24.1 ± 3.7 ($p=0.7$); mean total cholesterol was 192 ± 51.4 and 190 ± 42.3 ($p=0.8$); hypertensive patients were 21% and 24% ($p=0.3$); mean CD4 nadir was 242.8 ± 195.7 and 246.4 ± 167.7 cells/ μ l ($p=0.8$); duration of HIV infection was 12.8 ± 8 and 14 ± 8.6 months ($p=0.1$), respectively.

Predictors of all-cause mortality

Forty-one patients (5,68%) died during the follow-up. 9 (21.9%) for non-AIDS malignancy (prostate cancer, malignant melanoma, lung cancer, Hodgkin lymphoma, gastric cancer, pancreas cancer), 6 (14.6%) AIDS-related neoplasm (primitive cerebral neoplasm, Burkitt lymphoma, Kaposi's sarcoma), 8 (19.5%) vascular disease (myocardial infarct, stroke, pulmonary edema, other

organ infarct), 6 (14.6%) non-AIDS infection (sepsis, infective endocarditis, pneumonia), 10 (24.5%) liver disease, pulmonary disease (chronic obstructive pulmonary disease, pulmonary hypertension), 2 (4.9%) violent or accidental death (suicide, physical assault, trauma).

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