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Evaluation of psychoneuroimmunological interactions in HIV infected patients

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Abstract

HIV Infection has a wide clinical and prognostic variability, apparently depending on biological, psychological and psychosocial determinants, personal or contextual ones, and therefore can be a privileged field for research of the psychoneuroimmunological interactions.

The objective of this study is to evaluate some of the referred interactions, in a sample of 55 HIV1 positive patients and 30 healthy control subjects (N = 85).

Comparison between groups (t test) showed that patients exhibit a statistically significant greater emotional distress than controls, as well as an impairment in their quality of life. In medically stable and unstable patient groups, correlations between different level variables (Pearson correlations) showed psychoimmunological relationships which were apparently more clear in patients who will suffer a slower disease progression. These patients can be distinguished from the others with statistical significance, by levels of anxiety, depression, obsession/compulsion and sleep disturbance, as well as by the immune cell activation marker, CD25. Multiple regression analysis, using immune variables as dependent ones, confirms the importance of dimensions such as hostility, anxiety and stressors in determining immune variability.

In conclusion, we have found suggestive evidence relating the psychological factors and the immune response in HIV Infection.

***Key-words**: HIV infection; Psychological factors.*

INTRODUCTION

Psychoneuroimmunology in HIV infection has been subject of controversy, but recent investigations seem to clarify some of the complex relationships and some of the difficulties in this area [1,2].

Several studies have addressed the question of psychological stressors[3,4,5] bereavement and the immune function [6,7,8], as well as depression. In the case of depression, positive psychoimmunological relationships have been found [9,10,11,12], but also negative ones [13,14,15].

Social support has been described

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as an important mediating variable between social and existential stressors, adaptation, levels of emotional distress and quality of life, both in general forms as in the context of HIV infection[16,17,18].

Non-progressors or long-term survivors are, somehow, a particular population in which the course of infection is slower and the prognosis much more favourable than in the remaining.

In an attempt to understand clinical course variability related to the infection, attention has been paid to biological aspects of the host, the virus itself[19,20] and later to the psychological and behavioural aspects of these subjects [21,22,23], which might have important reflexes on neuroimmune modulation [24,25].

This can be a promising field of investigation, but we must keep in mind that testing a potential role for psychological dimensions in the evolution of HIV infection, implies the need of a careful choice of variables, both psychological and immunological ones. It also implies the need of controlling a number of confounding factors.

OBJECTIVES

Based on a psychosomatic approach, the large variability of the clinical evolution in HIV infection was investigated. Psychoneuroimmune network is the theoretical core in which psychological, immunological and psychosocial factors were evaluated in order to clarify the eventual relationships between these levels, in a longitudinal design.

This study is part of an ongoing research project in the context of the clinical activity in Consultation Liaison Psychiatry developed in the Infections Disease Department of a University Hospital (Santa Maria Hospital, Lisbon Medical School).

METHODS

Sample collection (N=85) involved a sub-sample of 55 HIV1 positive patients (G1) and another of 30 healthy control subjects (G2). Patients were followed in an Outpatient AIDS Clinic (Infectious Diseases Department, Santa Maria Hospital, Lisbon) and healthy controls were all voluntary blood donors in Lisbon Regional Centre, National Blood Institute. All subjects provided their informed consent before entering the study.

The following exclusion criteria were applied to patients: HIV diagnosis in less than 3 months, infectious or tumoral CNS pathology, recreational drug abuse in the 6 months prior to the study or during follow-up and cognitive deterioration or physical deterioration during follow-up. The follow-up period extended for 10 months, with distinct evaluations for patients (0, 3, 9 months) and healthy controls (0,3).

The patients' sub-sample was further divided into Stable and Unstable groups, based on the need for antiretroviral therapy change. Psychological assessments included:

– A semi-structured interview, designed to collect information about demographic characteristics, medical history and disease evolution, risk behaviours, initial reaction to HIV infection diagnosis, symptoms of psychological or physical distress, self evaluation in behavioural dimensions, future expectations and psychosocial support. It includes a short "stress factors scale"(FSTRESS) related to distressing events in the previous week, concerning physical or psychological health, professional, familiar, economical or social issues. The 6 items are rated 0-absent;1-mild; 2-moderate; 3-serious[26];
– Mini Mental State Examination (MMSE), a brief screening test to assess the cognitive state of patients [27];
– Hamilton Anxiety and Depression Rating Scales (HAMA, HAMD), to assess the clinical importance of anxiety and depression [28,29];
– Coping Mechanisms Scale (COP), a coping scale designed by our group, to investigate coping mechanisms associated to HIV infection and presented elsewhere [30];
– Catastrophic Cognitions Questionnaire-Modified (CCQ) to assess the danger evaluation associated with unpleasant emotions;
– Emotional Factor (F1), physical modifications – Physical Factor (F2) and intellectual difficulties — Mental Factor (F3). The total score is obtained by rating each item from 1 (no danger) to 5 (extremely dangerous)[31];
– Hopkins Symptoms Checklist (SCL90R), a multidimensional inventory to assess psychopathological symptoms. It is composed of 9 symptom dimensions: somatization (SOM), obsessive-compulsive (OBS), interpersonal sensitivity (IP), depression (DEP), anxiety (ANX), hostility (HOST), phobic anxiety (PHOB), paranoid ideation (PAR), psychoticism (PSC) and 3 indexes: general symptoms index (GSI), positive symptoms index (PSI) and number of positive symptoms (NPS)[32];
– Spielberg Trait or State Anxiety Inventory (STAI 1, 2), a self-evaluation instrument to measure state and trait anxiety[33];
– Nottingham Health Profile (NHP), a quality of life measure, evaluating the patient subjective perception about his health, with a total score and 6 dimensions – Energy, Pain, Emotional Reactions, Sleep, Social Isolation and Physical Mobility. Items are rated yes or no[34];
– Differential Inventory of Vitality States-(IDEA), which assesses the vitality of the subject, relating self awareness of energy, psychophysiological activation and the influence of pleasant or unpleasant feelings on mood, through 3 dimensions: the Activation Factor (IDEA1), the Stress

Factor (IDEA2) and the Arousal Factor (IDEA3)[35].

Immunological assessments included lymphocyte population differential counts, according to cluster differentiation (CD) antigens that characterise cell-surface molecules, using flow-cytometry. This immunoflourescence technique was performed on a cytometer *Cytoron Absolute, Ortho Diagnostics*. Antibodies were from *Trio-immunocount System, Ortho Diagnostics*. Analysis were performed in the AIDS National Reference Laboratory, Instituto Nacional de Saúde Dr Ricardo Jorge.

A 5 ml blood sample was collected from all subjects, always in the morning (8 –10h a.m.), after which they completed the psychological evaluation.

Immunological measurements included:

- CD 3+ (T cells)
- CD 19+ (B cells)
- CD 4+ (T Helper cells)
- CD 8+ (T Cytotoxic cells)
- CD 38+, CD 38+/8+ (activated cells)
- CD 45+RO+, CD 45+RO+/4+ (memory cells)
- CD 25+, CD 25+/3+ (activated cells, IL2 receptor α chain)
- CD 16+ (Natural Killer cells)
- Viral RNA, (nº of viral particles/ml in blood)

In this paper, we analyse data regarding only the first evaluation, for patient and control groups and we specifically evaluate psychoimmunological relations, leaving for further analysis the cognitive evaluation, the coping dimension, the psychosocial support and the quality of life. Statistical analysis included descriptive, Pearson correlations, *t* test and multiple regression analysis which were performed using SPSS (Statistical Package for Social Sciences).

RESULTS

Sample characterisation, according to sociodemographic variables, can be observed in Table I and II.

Table I - **Sex, marital status and ocupation category frequencies in both groups G1 and G2**

	G1 (55) %	*G2 (30)* %
Sex		
1 - Male	85.5	86.7
2 - Female	14.5	13.3
Marital status		
1 - Single	72.7	26.7
2 - Married	21.8	66.7
3 - Divorced	5.5	6.7
Ocupation		
1 - Unemployed	5.5	0
2 - Retired	3.6	0
3 - Unskilled labour	16.4	10.0
4 - Skilled labour	12.7	16.7
5 - Services	40.0	53.3
6 - Technical/superior	20.0	6.7
7 - Student	1.8	13.3

Using descriptive statistics, age and education (years) were analysed in both control and patients groups.

Table II - **Age and education in patient (G1) and control (G2) groups**

	Mean	*Sd*	*Min.*	*P25*	*P50*	*P75*	*Max.*
G1 (55)							
Age	37.71	10.29	20	30	35	46	62
Education	10.95	4.31	4	9	12	15	17
G2 (30)							
Age	38.60	12.89	19	27.5	40.5	48.25	60
Education	9.77	3.86	4	6.75	10	12	17

No significant differences were found between the two groups when comparing mean age and education (*t* test).

Age t = -.35 p* = .72
Education t = 1.25 p = .22
83 df (degrees of freedom)

Risk behaviours, time since diagnosis, staging and pharmacological treatments (psychopharmacological on antiretroviral ones) were also characterised. Alcohol and tobacco consumption were controlled in both groups (Table III).

Table III - **Sample characterization**

Risk behavior		%
– Homosexual		69.1
– Heterosexual		16.4
– IV drugs		14.5
Diagnosis		
– Stage A (non symptomatic infection)		41.8
– Stage B (symptomatic infection)		41.8
– Stage C (AIDS)		16.4
Time since diagnosis		
– ≤ 12 months		16.4
– 13-60 months		49.1
– > 60 months		34.5
(Mean – 51.3 months; sd 39.6)		
Psychiatric therapy		
– No therapy		70.9
– Therapy (psychological; pharmacological)		29.1
Antiretroviral therapy		
– No therapy		18.2
– 1 drug		25.5
– 2 drugs		54.5
– 3 drugs		1.8
Alcohol	**% Patients**	**Controls**
– No drinking	54.5	33.3
– Social drinking	40.0	60.0
– Heavy drinking	5.5	6.7
Tobacco		
– No smoking	40.0	53.3
– < 10 cigarettes/day	25.5	20.0
– ≥ 10 cigarettes/day	34.5	26.7

Descriptive statistics (mean values, standard deviation, minimum and maximum), regarding psychological and immunological variables, in controls and patients, are summarised in Tables IV and V.

Table IV - **Psychological variables. Descriptive statistics in controls and patients**

	Controls				Patients			
Variables	*Mean*	*sd.*	*Min.*	*Max.*	*Mean*	*sd.*	*Min.*	*Max.*
MMS					28.35	1.51	22.00	30.00
HAMA	6.63	3.76	1.00	15.00	12.29	10.38	0.00	32.00
HAMD	5.87	3.14	2.00	14.00	10.67	9.01	1.00	37.00
SCL SOM	0.47	0.43	0.00	1.58	0.70	0.60	0.00	2.50
SCL OBS	0.70	0.61	0.00	2.70	1.01	0.76	0.00	3.50
SCL IS	0.63	0.56	0.00	2.33	1.01	0.76	0.00	2.44
SCL DEP	0.48	0.49	0.00	2.23	0.96	0.73	0.00	2.54
SCL ANX	0.47	0.59	0.00	2.70	0.85	0.73	0.00	2.60
SCL HOST	0.58	0.73	0.00	3.17	0.82	0.81	0.00	3.17
SCL PHOB	0.21	0.53	0.00	2.71	0.52	0.64	0.00	2.57
SCL PAR	0.51	0.60	0.00	3.00	0.92	0.83	0.00	3.33
SCL PST	0.33	0.64	0.00	3.10	0.69	0.66	0.00	2.20
SCL GSI	0.46	0.49	0.03	2.51	0.86	0.63	0.01	2.33
SCL PSI	1.35	0.38	1.00	2.57	1.65	0.47	1.00	2.92
SCL NPS	29.43	22.08	3.00	88.00	43.16	24.87	1.00	88.00
CCQ T	62.33	12.74	44.00	86.00	65.16	17.08	21.00	105.00
CCQ F1	16.63	4.56	9.00	28.00	18.47	6.12	7.00	35.00
CCQ F2	21.67	5.19	14.00	31.00	22.84	5.89	7.00	35.00
CCQ F3	24.03	4.68	15.00	32.00	23.85	6.61	7.00	35.00
STAI 1	29.53	8.02	20.00	57.00	36.89	10.78	20.00	59.00
STAI 2	31.90	8.33	20.00	57.00	39.56	12.42	20.00	63.00
NHP GI	95.35	9.16	63.20	100.00	84.59	17.03	26.30	100.00
NHP EM	5.92	15.09	0.00	77.78	21.21	25.69	0.00	88.89
NHP EN	0.00	0.00	0.00	0.00	14.54	24.65	0.00	100.00
NHP P	5.00	14.90	0.00	75.00	6.59	16.64	0.00	62.50
NHP PM	3.33	9.81	0.00	50.00	8.41	12.28	0.00	62.50
NHP SI	8.66	15.48	0.00	60.00	25.45	31.14	0.00	100.00
NHP SP	2.67	10.15	0.00	40.00	20.36	29.69	0.00	100.00
IDEA 1	1013.93	49.00	895.00	1099.00	966.75	85.27	776.00	1104.00
IDEA 2	636.00	73.31	531.00	832.00	697.65	93.40	525.00	907.00
IDEA 3	692.17	131.98	524.00	1065.00	641.27	136.03	401.00	990.00

Table V - **Immunological variables. Descriptive statistics in controls and patients**

	Controls				Patients			
Variables	*Mean*	*sd.*	*Min.*	*Max.*	*Mean*	*sd.*	*Min.*	*Max.*
T Lymph.	2.124	536	1.083	3.227	2.076	616	595	3.052
CD 3	1.595	436	751	2.577	1.654	530	380	2.762
CD 4	931	349	473	1.876	468	273	62	1.186
CD 8	554	205	151	1.027	1.085	433	248	2.074
CD 16	204	102	46	413	207	135	69	868
CD 19	346	178	114	790	202	109	47	533
CD 25	14	12	0	57	6	6	0	28
CD 25/3	13	12	0	55	5	5	0	19
CD 38	819	327	174	1.454	314	173	73	907
CD 38/8	153	104	10	396	116	112	9	614
CD 45 RO	643	218	342	1.180	711	407	224	2.062
CD 45/4	440	172	225	893	209	116	6	456
ViralRNA					8.320	16.201	200	95.333

Mean values of immunological and psychological variables, in both groups, were compared (*t* test) and significant results can be seen in Tables VI and VII.

For all significant variables, except CD8, mean values were higher the in control group. For other immunological variables (T LINF, CD3, CD16, CD38/8 e CD45RO), the comparison of mean values between groups was not significant, but CD3, CD16 e CD45RO means were higher in patients.

Table VI - ***t* test. Immunological variables – patient/control groups**

Variables	*t*	*P*	*df*
CD4	-6.76	.000	83
CD8	7.66	.000	82
CD19	-4.03	.000	41
CD38	-7.89	.000	38
CD45RO4	-6.60	.000	44
CD25	-3.30	.000	36
CD25/3	-3.80	.000	35

Table VII - ***t* test. Psychological variables – patient/control groups**

Variable	*t*	*p*	*df*
HAMA	3.42	.001	76
HAMD	3.44	.001	73
SCL ANX	2.00	.050	88
SCL DEP	3.12	.002	86
SCL PAR	2.19	.03	85
SCL SI	2.38	.02	86
SCL GSI	2.72	.008	81
SCL PSI	2.79	.006	88
STAI 1	3.78	.000	86
STAI 2	3.65	.000	88
NHP GI	-4.01	.000	84
NHP EM	3.87	.000	86
NHP EN	4.38	.000	54
NHP PM	2.28	.02	85
NHP IS	2.98	.004	86
NHP SP	4.20	.000	70
IDEA 1	-2.63	.01	88
IDEA 2	3.14	.002	83

Psychopathological variables, whether they were significant or not

when comparing between groups, had higher values in patients, as would be expected.

The quality life index, from the Nottingham Health Profile (NHP GI), was superior in controls, as well as the Activation Factor from the Differential Inventory of Vitality States (IDEA 1). The Nottingham Health Profile subscales (NHP- EM, EN, PM, SI e SP), which express impairment in different dimensions of quality of life, were higher in patients.

Patients were further divided in *stable* and *unstable* groups, according to the need of changes in antiretroviral therapy. The *stable group* (N = 32) included subjects who remained in the same therapy (antiretroviral drugs) during the follow-up period and the *unstable group* (N = 23) included those who had suffered any modification in therapeutic regimen due to a clinical or immunological impairment, during follow-up. We must note that, at the time of the evaluation, neither patients nor investigators knew which of them would be classified as *stable* or *unstable*.

Using *t* test, we compared both groups regarding immunological and psychological dimensions. Significant results can be observed in Table VIII.

The SCL 90 R obsessive thoughts dimension (SCL OBS), the Hamilton anxiety and depression scales (HAMA, HAMD) and the NHP sleep dimension (NHP SP) were higher in *unstable* patients, as well as CD25 mean value.

Table VIII - **Immunological and psychological variables – stable/unstable patients**

Variables	*T*	*p*	*df*
CD25	2.11	.04	30
HAMA	2.31	.03	34
HAMD	2.09	.05	34
SCL OBS	2.02	.05	53
NHP SP	2.07	.05	35

We must remark that time since diagnosis, age and education were not significantly different when comparing between groups:

Time	t .71	p .48	53 df
Age	t -.35	p .73	53 df
Education	t -.61	p .54	53 df

Viral RNA variable (number of viral particles per ml/blood or viral load) was significant when comparing between groups, using *t* test and Mann Whitney (non-parametric test) and higher values were found in the *unstable* group:

Viral RNA	t 2.36	p .02	53df	(t test)
	U 97.36	p .000		(Mann Whitney)

Correlation analysis between psychological and immunological variables in each group, can be observed in Tables IX and X.

Table IX - **Unstable patients – significant correlations (Pearson)**

	Unstable patients						
	CD3	***CD8***	***CD19***	***CD38/8***	***CD45RO***	***CD45/4***	***CD25***
CCQ T			-.47*				
CCQ F1			-.52*				
CCQ F2			-.56**				
SCL ANX					.50*		
SCL FOB		.45*			.58**		
SCL OBS				.42*	.49*		-.42*
SCL SOM					.54**		
SCL GSI					.45*		
SCL PSI					.49*		
NHP GI						-.42*	
NHP SI	.45*	.45*			.62**	.49*	
IDEA 2					.49*		

*$p \leq .05$; **$p \leq .01$

– Viral RNA was not correlated with any psychological variable in this group (*unstable* patients).

Table X - **Stable patients – significant correlations (Pearson)**

	CD19	**CD16**	**CD38**
STAI 1	-.42*	-.38*	-.35*
IDEA 2		-.37*	

* $p \leq .05$; ** $p \leq .01$

– In *stable* patients, we can observe positive correlations between viral RNA and the following variables:

STRESSF (.47**); HAMD (.45**)
SCL ANX (.36*); SCL PHOB (.59**)
SCL OBS (.41*); SCL PAR (.35*).

MULTIPLE REGRESSION ANALYSIS

Multiple regression analysis uses the correlations between a set of independent variables and one dependent variable and by attributing independent variables a coefficient, we can create a predictive equation, the regression equation [36].

In this study regression analysis was used to explain the immunological variables, as dependent ones, in function of psychological variables and 4 "dummy" variables – diagnosis, time since diagnosis, antiretroviral therapy and psychiatric therapy.

Immunological variables included in regression were:

CD4, CD8, CD19, CD16, CD38, CD38/8, CD45RO, CD45RO/4, CD25, CD25/3.

Psychological variables included in regression were:

STRESSF, HAMA, HAMD
CCQF1, CCQF2, CCQF3
SCL DEP, SCL HOST, SCL GSI, SCL NPS, SCL PSI
STAI1, STAI2, NHP GI
IDEA1, IDEA2 and IDEA3.

Calculating **f critical value (f = 1.65)**, immunologic variables explained in the regression equation, were:

CD4 (f 4.53 p=.000) CD8 (f 3.17 p=.000)
CD19 (f 2.04 p=.009) CD38/8 (f 2.09 p=.007)
CD45RO (f 2.99 p=.000) CD45RO/4 (f 4.18 p=.000).

CD16, CD38, CD25 and CD25/3 were not explained in regression (F< 1.65).

Calculating **t critical value (t = |1.98|)**, independent variables which contribute to explain each dependent variable, were as following:

• CD4 (R^2 = .40-40% variance)
DIAG B (β -167.56; t -2.63**;** p.01),
DIAG C (β -312.67; t -3.90**;** p.000)
TERI 2 (β -165.87; t-2.18**;** p.03),
TERI 3 (β -257.31; t -3.11**;** p.002).

• CD8 (R^2 = .32-32% variance)
DIAG B (β 418.5; t -3.58; p.000),
TERP (β 254.67- **t** 2.69- p.008)
F STRESS- (β 38.15; t 2.27; p.03),
SCL HOST (β 454.53- **t** -4.31- p.000)
SCL GSI- (ß 789.95; t 3.09; p.002).

• CD19 (R^2 = .23-23% variance) TERI 2 (β -98.13; t -2.68; p.008),
SCL HOST (β -55.54; t -2.01; p .05),
SCL GSI (β 155.16; t -2.32; p .02),
SCL PSI (β -84.33; t -2.23; p .03).

• CD38/8 (R^2 = .24 - 24% variance)
TERI 2 (β -81.09; t -2.17; p .03),
TERP (β 57.28; t 2.26; p .03),
SCL HOST (β -82.01; t -2.91; p .004).

• CD45RO (R^2= .21-21% variance)
DIAG B (β -296.99; t -2.70; p.008),
TERI 2 (β -298.47; t -2.27; p .03),
TERP (β 250.06; t 2.81; p.006),
HAMA (β -18.80; t -2.27; p .03),
SCL HOST (β -343.30; t -3.46; p.001)
SCL GSI (β 522.94; t 2.18; p.03).

• CD45RO/4 (R^2 = .24-24% variance)
DIAG B (β -128.41; t -4.28; p.000),
DIAG C (β -188.13; t -4.97; p.000).

Notation represents:

– DIAG B and C - staging:
B - Symptomatic Infection ;
C - AIDS;
– TERI 2 and 3 - antiretroviral therapy, 2 or 3 medications;
– TERP - psychiatric therapy;
– SCL HOST, SCLGSI, SCLPSI - SCL90R hostility scale, general symptoms index, positive symptoms index ;
– HAMA - total *score* from Hamilton Anxiety Rating Scale.

DISCUSSION

This patient sample is composed by a group of well educated adults,

mostly homosexual men which reflects the dominant risk behaviour at that time. The mean time since diagnosis is almost 5 years, only 16.4% of the patients had AIDS. The majority of them are on antiretroviral therapy including 2 drugs, which can be explained because at the time of the first evaluation, Highly Active Antiretroviral Therapy (HAART) was in the beginning. Only 29.1% of the sample needed psychological or psychiatric support and heavy drinking was present in a minority of cases (5.5%); 65.5% of them did not smoke or smoked less than 10 cigarettes a day.

The control group is matched with patients concerning age, sex and education. The health status of this group was granted by the clinical screening of blood donors. Their behaviour was similar to patients regarding tobacco and alcohol consumption.

The descriptive statistics of psychological variables, showed that patients had higher mean values in all psychopathological dimensions, a slightly more catastrophic evaluation of physical, emotional and mental dangerous events, an impairment in quality of life, in general and in NHP dimensions when compared to controls. The results of IDEA (Vitality States Inventory) indicated a state of well-being in both groups, but levels of activation were higher in controls, meaning they were more interested in environmental events and actions.

The results of groups comparison were statistically significant in the majority of variables that express dimensions of emotional distress, but they did not differ significantly in cognitive evaluation of dangerous events. Mean comparisons in quality of life dimensions and general index were all significant, except in the pain dimension which showed very low values in both groups.

As to immunological variables, mean values were, in general, higher in controls, except for CD3+, CD8+, CD16+ and CD45RO+. The significant results obtained in group comparison clearly reveal the drop in CD4+ cells and the rise in CD8+ cells in patients and the CD4/CD8 relation was 0.4 in patients and 1.7 in controls. Those are expected results according to the damage HIV produces in the immune system, even in non symptomatic infection. The other significant results concerned B cells, activated and memory cells. Most published references mention the rise in activation markers such as CD38+ and CD25+ during the course of the infection, and in early or intermediate phases the rise of memory cells, which will drop latter. Activation markers can be considered surrogate markers of the evolution and HAART response [37,38,39].

According to the patterns displayed by this group of patients, they can be included in an intermediate phase of the HIV infection.

Immunological variables in controls were within the normal range.

The definition of 2 different groups among patients included the knowledge of the need to change antiretroviral therapy, during the follow-up period. Therefore, this evolutive dimen-

sion can be later applied to the whole sample, thus allowing definition of the *stable* and the *unstable* groups.

Comparison between these groups, using *t* test, reveals that significant differences occur in psychological dimensions such as anxiety, depression (Hamilton Rating Scales) obsession--compulsion (SCL90R) and sleep disturbance (NHP) with higher means in *unstable* patients, from the first time of evaluation. There were no significant differences in age, education or length of time since diagnosis, between *stable* and *unstable* patients. CD25+ was the only significant immunological variable in group comparison.

Therefore, one can hypothesize that anxiety, depression, rigidity or affective isolation associated to obsessive dimensions, might be vulnerability factors that interact with biological variables (from the host and the virus), determining disease progression.

Higher values of viral RNA and CD25+ suggest a more evident progression of the infection in *unstable* patients.

The correlation pattern observed in each group showed some further differences. In the *unstable group*, there are positive correlations between memory cells, T cytotoxic cells (CD8+), T lymphocytes and indicators of emotional distress, as well as negative correlations between B cells and cognitive evaluation or CD25+ cells and the obsession dimension. Viral RNA does not correlate with any of the studied variables.

As for the *stable group*, despite the lower number of correlations, these seem to make sense: B cells, NK cells and CD38+ activated cells all correlates negatively with anxiety states measured by STAI ; NK cells also correlate negatively with Stress Factor from IDEA and viral RNA correlates positively with stress factor scale from the interview, anxiety (Hamilton and SCL90R), phobic anxiety, obsessive/ /compulsive and paranoid ideation from SCL90R.

In a more active viral replication phase (*unstable*), the biologic dimension in the immune response is perhaps determinant, and one can presume that the psychoimmune relationships might be "blunted", as we have found comparing healthy controls and patients [26].

The multiple regression analysis showed that psychological dimensions such as hostility partially explain the variance of immune cells such as CD8+; CD19+ ; CD38+/8+ and CD45RO, or cytotoxic lymphocytes, B cells, activated T cells and memory cells. The same is also evident in other dimensions like anxiety, general symptoms index, positive symptoms index and stress factor scale.

CONCLUSION

Sample size implies caution in interpreting and inferring from the results, particularly those from *stable* and *unstable* groups. When one finds some apparent vulnerability factors such as signs of emotional distress, one must ask what would be the mediating variables between them and the immune system functioning in healthy subjects and in patients.

The neurochemical link is becoming clearer, but at a psychological or psychosocial still level, confounding variables are still an important problem.

One can hypothesize that emotional, cognitive or immune system "distress" might generate a neurochemical dysfunctional pattern that can be considered "cause and effect" of many pathological manifestations. Modulating factors such as life events, social support, coping or personality variables, would interact in a positive or negative way to explain the clinical variability of disease, like HIV Infection. Our results are in agreement with such hypothesis.

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