High prevalence of undiagnosed anxiety symptoms among HIV-positive individuals on cART: a cross-sectional study

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Abstract. – **INTRODUCTION:** Anxiety disorders are frequent in HIV-infected individuals, can pre-exist or occur during HIV infection. We evaluated with a self-reported questionnaire whether anxiety is related to HIV clinical status and therapeutic success in a cohort of HIV-positive subjects in Sicily.

PATIENTS AND METHODS: We enrolled 251 patients on combination antiretroviral therapy (cART) for at least six months; Self Rating Anxiety State SAS 054 was used to diagnose anxiety and a Z score ≥ 45 points was considered diagnostic.

RESULTS: 47% of patients were diagnosed with anxiety. Patients showing symptoms related to anxiety had experienced a high number of therapeutic switches (fourth line or more).

CONCLUSIONS: These data confirm a high prevalence of anxiety symptoms among subjects with HIV infection in Eastern Sicily. Physicians should be aware of the extent of the problem and should be able to adequately manage anxiety in the setting of HIV infection.

Key Words:
  HIV, Anxiety, cART.

Introduction

The introduction of combination antiretroviral therapy (cART) has transformed Human Immunodeficiency Virus (HIV) infection into a chronic disease[1]. However, cART is not able to eradicate HIV infection[2-15]. As a consequence of aging, HIV-infected patients are experiencing several non-AIDS-associated morbidities, including diabetes mellitus, malignancies, cardiovascular disease, osteoporosis and neurocognitive disorders[16-51].

Anxiety, panic attacks, major depressive disorders and dysthymia are highly prevalent in HIV-1-infected individuals and are almost three times more frequent in people living with HIV/AIDS as compared to the general population[52].

The prevalence of anxiety is as high as 38% in clinical studies and it is often associated with depression[53-57]. Anxiety may pre-exist to HIV infection or it may be related to risk behaviours for HIV infection (i.e. unsafe sex or drug use); in addition, patients may feel anxious at time of or after HIV diagnosis because of the fear of the unknown, HIV-related stigma, death. Key moments in the personal and social life of HIV-positive subjects (i.e. the decision to disclosure HIV diagnosis to relatives, partner and friends, desire of parenthood, decisions dealing with sexual activity) may determine isolation and mental illness[58]. In addition, non-HIV-related stigma, i.e. homophobia or unsafe social and economic status, should be considered[59,60]. In presence of depressive and/or anxiety symptoms, patients often refuse to access to social support and to seek treatment[58]. In fact, antiretroviral treatment adherence among patients with anxiety and/or depression has been reported to be poor[55,58,61,62].

The relationship between anxiety and viro-immunological responses is still unclear. While the presence of HIV-related signs or symptoms may

represent a major source of stress and then a trigger for anxiety[63], the presence of stress has been associated with faster HIV progression to AIDS[64].

The aim of this study was to investigate the prevalence of symptoms related to anxiety in a cohort of HIV-positive patients on combination antiretroviral therapy (cART) and to evaluate the association between anxiety symptoms and some socio-demographic and clinical parameters.

Patients and Methods

Study Participants

A cross-sectional study was performed on 251 consecutive patients on cART for at least six months, followed at two different AIDS Outpatient Units in Catania and one in Messina, Sicily (Italy). Patients treated for a previous known diagnosis of anxiety or depression and subjects involved in active use of illicit intravenous drugs in the previous six months were excluded. All patients gave their written informed consent prior to enrolment.

Socio-demographics (age, sex, HIV transmission risk, employment and partner status) and clinical parameters (HIV RNA viral load, CD4+ T-cell count, CDC stage, time from infection and length of antiretroviral exposure, number of therapeutic lines (first line, second or third, fourth or more)), comorbidities (HBV or HCV coinfection), use of a drug potentially affecting the central nervous system (CNS) such as efavirenz (EFV), were collected from medical records at the time of test administration.

All subjects were submitted to a validated questionnaire to detect the presence of sign or symptoms related to anxiety. The Self Rating Anxiety State SAS 054, a self-submitted test exploring last week symptoms, was used for screening.

The Self Rating Anxiety State SAS 054 consists of:

• 15 items exploring sympathetic symptoms (palpitations, accelerated heart rate, sweating, nausea, shortness of breath, paresthesias) and symptoms of post-traumatic stress disorders (PTSD), such as panic attacks, sleep disorders, nightmares;
• 5 items exploring the well-being status.

A score from 1 to 4 was assigned to each answer (never, sometime, frequently and always). The total raw scores range from 20 to 80. The crude score was then converted into a standard score ($n + n/4$ = z score). The clinical interpretation of anxiety index score is reported below: 20-44: normal range; 45-59: mild or moderate anxiety levels; 60-74: marked or severe anxiety levels; 75 and over: extreme anxiety levels. According to test procedures, we considered "anxious" all patients with a Z score $\geq$ 45 points[65-67].

Information about historical low adherence (documented self-reported discontinuation or drug holidays, self-reduced pill burden, irregular drug refill) were collected by review of medical records.

The primary endpoint was to evaluate the prevalence of anxiety symptoms. The secondary endpoint was to correlate these symptoms with socio-demographic and clinical factors.

Statistics

Categorical variables are presented as number of cases (percentage) and were compared by the χ^2 test or Fisher's exact test, when appropriate. Continuous variables are expressed as median (interquartile range, IQR) and were compared by Mann-Whitney test. Identified variables in the univariate analyses with a p-value less than 0.05 were included in the logistic regression model to determine the relationship between the dependent variable (anxiety) and independent variables such as demographic, clinical and social factors. Statistical significance was defined as $p < 0.05$.

Results

Demographic and Viro-Immunological Characteristics of Study Population

Of the 251 patients included in this analysis, 171 (68.1%) were men and the median age was 43 (IQR 37-49) years. 57 (22.7%) were infected by intravenous drug use (IVDU), 75 (29.9%) were men having sex with men (MSM), 110 (43.8%) were heterosexual. 67 (26.7%) were HCV and/or HBV co-infected. 155 (61.8%) were married or had a stable partner, 158 (62.9%) were employed.

Median CD4+ T-cell count was 479 (IQR 289-764) cells/μl, HIV-1 RNA viral load was < 50 copies/ml in 201 patients (80.1%). 77 (30.7%) had a previous AIDS diagnosis (CDC stage C), 124 (49.4%) were asymptomatic (CDC A). Median time from diagnosis was 192 (IQR 132-228) months, median duration of cART was 114.4 (IQR 60-158.7) months. 55 (21.9%) were on first line cART regimen, 94 (37.4%) were on second or third line of therapy and 102 (40.6%) were on fourth line or more. 68 (27.1%) were taking an EFV-containing regimen at the time of enrolment. 62 (24.7%) had documented historical suboptimal adherence to cART.

Please refer to Table I for additional demographic and clinical characteristics.

Anxiety Symptoms

118 subjects (47%) achieved a z score ≥ 45, that was suggestive of anxiety according with test procedures. The two groups (patients with or without anxiety) did not differ significantly on sex, age, employment and marriage status, years of cART exposure, historical adherence to cART, CD4+ T-cell count, HIV-1 RNA plasma viral load and time from HIV-1 diagnosis, having been symptomatic (CDC B and C) or having had a previous AIDS diagnosis (CDC C). When comparing subjects with or without anxiety according to HIV transmission risk, a higher percentage of IVDU was found among anxious patients (31.4% *vs.* 15%, *p* = 0.001). Patients with HCV and/or HBV co-infection represented 21.1% in the group of patients without anxiety, but 33.1% in the anxiety group (*p* = 0.032).

The prevalence of anxiety symptoms was lower among patients currently taking EFV: 32.3% of subjects without anxiety were currently receiving EFV *vs.* 21.2% of those belonging to the anxiety group (*p* = 0.047).

Patients who had experienced a higher number of therapeutic switches had more frequently a z score ≥ 45: in fact, 53.4% of anxious patients were on fourth line or more *vs.* 29.3% of those without anxiety (*p* = 0.002).

In the multivariate analysis, a high number of therapeutic switches (fourth line or more) (*p* = 0.02) was still associated with anxiety (see Table II).

Discussion

The long-term efficacy of antiretroviral treatment has radically modified the prognosis and quality of life of HIV-infected subjects. In fact, HIV infection has become a chronically treatable condition; nevertheless, people living with HIV frequently have difficulties to accept their condition, because of the fear of discrimination and worries about long-term prognosis, tolerability and efficacy of treatment[58].

Anxiety and depression are highly prevalent among HIV-infected subjects and are the most common and often underestimated psychiatric disorders. The link between anxiety and depression is well established and their symptoms may often overlap[55,68-70]. Moreover, the self-administered questionnaire could not accurately discriminate between anxiety and depression[68-70].

In our cohort, 47% of patients showed anxiety-related symptoms, which is around the estimated prevalence among HIV-positive patients (as high as 38%)[53-57], but higher than the prevalence rates reported by Olagunju et al (21.7%)[71] and Vitiello et al (20.3%)[72]. In the univariate analysis patients with anxiety were more frequently IVDU. The social and psychophysical "burden" of illicit drug use, as well as the presence of infectious comorbidities, i.e. HCV infection, might favour the development of anxiety symptoms in this subgroup of patients. As active IVDU have been excluded from analysis, it may be hypothesized that subjects with a previous history of illicit drug use should still have some long-term problems that affect their social and psychological health. It cannot be excluded that in some cases drug use may represent a sort of self-medication to pre-existing anxiety disorders[73], however logistic regression did not confirm this correlation. It has been shown that being unemployed may correlate with anxiety symptoms[55,71]; in the present study, however, we did not find any significant association between anxiety and employment status.

Table I. Characteristics of study participants.

	N = 251
Age (years)**	43 (37-49)
Sex: male/female*	171 (68.1)/80 (31.9)
Employment status (employed/unemployed)*	158 (62.9)/93 (37.1)
Duration since HIV diagnosis (months)**	192 (132-228)
HIV risk	
Homosexual*	75 (29.9)
IVDU*	57 (22.7)
Heterosexual*	110 (43.8)
Other*	9 (3.6)
Hepatitis B/C virus coinfection*	67 (26.7)
HIV stage (1993 CDC criteria)	
A*	124 (49.4)
B*	50 (19.9)
C*	77 (30.7)
CD4+ T-cell count (cells/µl)**	479 (289-764)
HIV RNA viral load <400 copies/ml*	212 (84.5)
Duration of cART (months)**	114.4 (60-158.7)
cART I line*	55 (21.9)
II-III line*	941 (37.4)
IV line or more*	102 (40.6)
Current EFV use*	68 (27.1)
Suboptimal adherence to cART*	62 (24.7)

*Data presented as N (%) **Data presented as median (IQR)

Table II. Distribution of patients with or without anxiety according to socio-demographic and clinical parameters.

	Patients with anxiety N = 118 (47%)	Patients without anxiety N = 133 (53%)	p^{α}	p^{β}
Age (years)**	43 (27-49)	44 (38-52)		
Gender (Male/Female)*	80 (67.8)/38 (32.2)	91 (68.4)/42 (31.6)		
Employment status (Employed/ Unemployed)*	50 (42.4)	43 (32.3)		
Duration since HIV diagnosis (months)**	198 (123-228)	180 (132-228)		
HIV risk				
Homosexual*	29 (24.6)	46 (34.6)		
IVDU*	37 (31.4)	20 (15)	$p = 0.001$	
Heterosexual*	52 (44.1)	58 (43.6)		
Other*	0 (0)	9 (6.8)		
Hepatitis B/C virus coinfection*	39 (33.1)	28 (21.1)	$p = 0.032$	
HIV stage (1993 CDC criteria)				
A*	56 (47.5)	68 (51.1)		
B*	32 (27.1)	18 (13.5)		
C*	30 (25.4)	47 (35.3)		
CD4 T-cell count (cells/µl)**	486 (305-757)	476 (278-771)		
HIV RNA viral load <400 copies/ml*	97 (82.2)	115 (86.5)		
Duration of cART (months)**	120 (48-163)	110 (61-156)		
cART I line*	21 (17.8)	34 (25.6)		
II-III line*	34 (28.8)	60 (45.1)		
IV line or more*	63 (53.4)	39 (29.3)	$p = 0.002$	$p = 0.02$
Current EFV use*	25 (21.2)	43 (32.3)	$p = 0.047$	
Adherence to cART*	88 (74.6)	101 (75.9)		

*Data presented as N (%) **Data presented as median (IQR) $^{\alpha}$Univariate analysis $^{\beta}$Multivariate analysis
cART: combination antiretroviral therapy; EFV: efavirenz; IVDU: intravenous drug use

Of note, the number of therapeutic failures was significantly higher among patients with anxiety. The number of therapeutic lines is generally related to low tolerability or virological failure and the latter should be an epiphenomenon of low adherence. It is difficult to establish whether it is the therapeutic failure that leads to anxiety or it is anxiety that reduces adherence to cART, causing therapeutic failures and, eventually, disease progression. Even if several authors reported low adherence to cART among anxious patients[55,58,61,62], we did not detect any difference in historical documented adherence between patients who were anxious and those who were not.

Our findings suggest the need for screening and treatment of patients with anxiety disorders, to prevent therapeutic failures, low adherence and poor outcomes, especially during some critical issues (diagnosis, HIV disclosure, clinical progression, switch of therapy) when coexisting unstable social and economic status may amplify some symptoms. HIV treating clinicians should be aware of the extent of the problem and be able to properly diagnose and treat anxiety.

Our study has some limitations. Firstly, it is a cross-sectional one: anxiety, as depression, changes over time, as such, causality could not be established. Secondly, considering that symptoms of anxiety and depression are often associated, a parallel screening for depression would have been worthy to better characterize the profile of psychological distress in patients with HIV infection.

Conclusions

The prevalence of anxiety symptoms was high in our cohort of HIV-positive subjects on cART. Considering that anxiety was associated with a great number of therapeutic switches, psychological support may have a crucial role in patients with HIV infection, especially for those with advanced disease and therapeutic failures. Prospective studies on large cohorts are needed to establish the causal relationship between anxiety, socio-demographic and viro-immunological factors. In addition, future research should evaluate the effectiveness of different psychological strategies aiming at reducing or better controlling the impact of anxiety symptoms in HIV-infected subjects[64,74].

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Competing Interest

None.

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