Short communication

Incidence, medical and socio-behavioural predictors of psychiatric events in an 11-year follow-up of HIV-infected patients on antiretroviral therapy

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Background: Psychiatric disorders are relatively common among HIV-infected patients. However, there are few studies about their potential risk factors. This analysis aimed to measure the incidence of severe psychiatric events (PE) among patients receiving combination antiretroviral therapy (cART) of the French APROCO-COPILOTE (ANRS CO8) cohort, and to identify the medical and socio-behavioural correlates of their first episode of depression, suicide or suicide attempt (D/S/SA).

Methods: APROCO-COPILOTE is a cohort of patients started on a protease inhibitor regimen between 1997 and 1999, with prospective medical standardized records and self-administered questionnaires collecting socio-demographic and socio-behavioural data. This analysis included all 11-year follow-up visits for 1,095 patients having completed baseline self-administered questionnaires. A proportional hazard Cox model was used to identify the correlates of a first D/S/SA event.

Results: The overall prevalence of severe PE remained low: 50 patients experienced 67 events (incidence rate [95% CI] = 1.04 [0.82, 1.32] per 100 person-years). Depression (n=16), suicides (n=5) and suicide attempts (n=14) were the most frequently diagnosed PE (0.54 [0.39, 0.76] per 100 person-years) among 25 patients. Multivariate results showed that unemployment, unstable housing, detectable viral load and smoking more than 20 cigarettes/day were independently associated with D/S/SA.

Conclusions: Although the incidence of severe PE remained relatively low among the patients of APROCO-COPILOTE cohort, this study’s results underline a clinically important problem in HIV-infected patients receiving cART. Furthermore, our findings not only emphasize the importance of comprehensive care, especially for socially vulnerable patients, but may also help future studies designed to assess the effectiveness of interventions in reducing the risk of PE during cART.

Introduction

Psychiatric disorders are common among HIV-infected individuals [1] and are the second leading cause of hospitalization after opportunistic infections in combination antiretroviral therapy (cART)-treated HIV-infected patients [2]. HIV-infected patients are 2–7× more likely to meet criteria for major depressive
disorder than the general population [3]. Suicide attempts and suicidal ideation, a proxy of depression, are also more frequent than in the general population [4] and are associated with the severity of depression [5]. Adequate monitoring of psychiatric symptoms is still uncommon in clinical follow-up of HIV-infected patients. What generally happens is that only the most critical psychiatric events, requiring hospitalization or urgent clinical management, are recorded. However these events represent only the ‘tip of the iceberg’ of all psychiatric events occurring in this population. Therefore, focusing on these events and their possible risk factors during cART follow-up can provide important information about how and why they occur.

The aim of this study was to measure the incidence of severe or life-threatening psychiatric events in a large, multicentre, prospective cohort of HIV-infected patients receiving long-term cART, and to determine the HIV-related and socio-behavioural factors independently associated with the occurrence of these events. The study focused particularly on the investigation of three types of events: depression, suicides and suicide attempts (D/S/SA).

Methods
Data collection
APROCO-COPILOTE (ANRS CO8) is a French cohort set up between 1997 and 1999 to study clinical, immunological, virological and socio-behavioural follow-up in HIV-infected patients started on a cART which included at least one protease inhibitor (PI). Patients were enrolled at cART initiation and had clinical and biological follow-up visits at baseline (M0), at 1 and 4 months (M1, M4), and every 4 months thereafter. Standardized clinical and biological data – including CD4+ T-cell count, viral load, CDC clinical stage, HIV transmission group, antiretroviral naïvety at baseline and HCV infection – were collected at each visit by means of a medical questionnaire filled out by the prescribing physician. Data about patients’ sociodemographic and socio-behavioural characteristics – including age, gender, stability of housing, education, employment, presence of steady partner, social support, alcohol and tobacco consumption, quality of life, adherence to cART and physician–patient relationship – were collected by self-administered questionnaires at inclusion, at M1, M4, M12 and every 8 months during the first 5 years of follow-up, then yearly thereafter. These characteristics of the patients have been described in detail elsewhere [6,7].

Psychiatric events measurement
During follow-up, all HIV-related events according to the CDC classification system [8] and other clinical and laboratory severe events were prospectively recorded. An event was considered as severe when it required medical intervention, hospitalization or an extension of hospitalization, when it led to a life-threatening condition (that is, grade 3 or 4 according to the National Agency for Research on AIDS and Viral Hepatitis [ANRS] scale for grading severity of adverse events in adults [9]), or when it resulted in death. In particular for psychiatric disorders, grade 3 events cover, according to the ANRS scale, ‘major anxiety or confirmed depressive episode requiring treatment’, and grade 4 events cover ‘acute psychosis requiring hospitalization, including suicidal ideation, manic state, and hallucinatory delusion’. A Validation Committee, composed of clinicians, methodologists and pharmacologists, re-evaluated the severity of each clinical event documented in patients’ medical records. In addition, a psychiatrist (LM) analysed and validated the events used as outcome. The following severe events were selected for this analysis: depression, suicide and suicide attempt.

Statistical analyses
Time to an event was calculated in days from the date of PI-containing cART initiation. Incidence rate of D/S/SA events was estimated as the number of cases divided by the number of person-years (PY) of follow-up, first by considering all events occurring during follow-up for the selected patients, and second by considering only the first event occurring for each patient. In this second case, the follow-up of patients experiencing D/S/SA events was censored after the date of the first event, death for any reason other than suicide, or last scheduled visit, whichever occurred first.

Potential correlates of the occurrence of the first D/S/SA event were studied using a Cox proportional hazards regression model including fixed and time-varying factors. For time-varying factors, the last known value was carried forward in the case of missing data at a scheduled visit. In the case of an event occurring between two consecutive follow-up visits, the values for the time-varying variables measured at the visit preceding the event were used. Among the clinical characteristics recorded during follow-up, undetectable plasma HIV RNA, CD4+ T-cell count and adherence to cART were treated as time-varying variables. All sociodemographic and socio-behavioural characteristics were treated as time-varying variables, with the exception of gender, age, education level and quality of life, which were measured at baseline. Variables with a P-value <0.20 in the corresponding univariate Cox model were considered as eligible for the initial multivariate Cox model, except for gender, age and baseline mental quality of life, which were introduced into the multivariate model to reduce
possible confounding factor bias. A backward stepwise procedure retaining only significant variables according to the Wald test \( P<0.05 \) was then used to build the final multivariate model. A residual analysis for outlier detection did not alter the results of the multivariate model. All statistical analyses were performed using Stata 10 software [10].

**Results**

All 1,095 patients who completed the self-administered questionnaire at enrolment were selected for this study. Among them, 496 patients (45.3%) dropped out from the cohort before their last scheduled visit, for the following reasons: 170 patients withdrew from the study, 113 died and 213 were lost to follow-up. The median (IQR) and total time of follow-up was of 6.1 (2.0–9.8) years and 6,343.4 PY, respectively.

The distribution of psychiatric events among the selected patients is described in Table 1. The total number of psychiatric events was 67 among 50 patients, with an incidence rate (95% CI) of 1.04 (0.82, 1.32) per 100 PY. Among these, depression \( n=16 \) events, suicide \( n=5 \) and suicide attempt \( n=13 \) were the most frequently reported psychiatric events and concerned 25 of the cohort’s patients (the incidence rate [95% CI] of these events was 0.54 [0.39, 0.76] per 100 PY). The incidence rate (95% CI) of the first D/S/SA event was 0.39 (0.27, 0.58) per 100 PY.

The characteristics of the selected patients and the results of univariate and multivariate analyses are detailed in Table 2. Social support from one’s steady partner, high adherence to cART, low alcohol consumption and CD4+ T-cell count were all associated with lower risk of D/S/SA only in univariate analyses. No significant association was found between smoking cessation and the risk of a PE or a D/S/SA. The following variables were independently associated with a lower risk of a first D/S/SA event: stable housing (adjusted hazard ratio [AHR; 95% CI] =0.37 [0.15, 0.93]), being employed (0.37 [0.14, 0.99]) and having an undetectable viral load (0.21 [0.08, 0.59]). Moreover, smoking more than 20 cigarettes per day (2.96 [1.23, 7.11]) was independently associated with a higher risk of a first D/S/SA event. The analysis was adjusted for gender, age and a mental quality of life at baseline, comparable (Mental Component Summary [MCS] score > the 25th percentile of the distribution in general population of same gender and age) with that of the general population.

**Discussion**

In this cohort study of 1,095 HIV-infected patients receiving cART, the incidence of severe or life-threatening psychiatric disorders remains low. Factors reflecting good social status (employment and stable housing) and HIV clinical status (undetectable viral load) protect against the occurrence of D/S/SA. On the contrary, heavy smoking was found to be associated with a higher risk of these events. Other studies have already highlighted that heavy smoking is significantly and independently associated with suicidal risk [11] and depression [12] in the general population, confirming that this association is not specific to HIV disease. The primary explanations for this association between smoking and depression/suicide are their common causes, but may involve other factors [13].

Smoking prevalence and dependency is higher in HIV-infected patients than in the general population [14]. While interventions for reducing or quitting smoking are strongly recommended for the former because of their increased risk of cardiovascular diseases and lung cancer, results from studies reporting on the effectiveness of such interventions are not consistent [15].

Changes in social conditions are also crucial in HIV-infected patients. Patients with stable employment have been shown to present a decreased risk of hospitalization or death compared with those with temporary employment, independently of the classic determinants of HIV-infected patients’ health status [16]. Although it has been reported that unemployment is associated with a higher prevalence of depression [17], their causal relationship remains unclear. Access to mental health services has been associated with return to work and improved well-being [17]. Unstable housing conditions have been associated with poor mental health and depression [18], but also with lower medication adherence, lower utilization of health and social services, poorer health status and increase in HIV risky behaviours [19]. Interventions focused on providing stable housing conditions can improve mental health and reduce depression in HIV-infected patients [20]. Consequently, such interventions may be the first step in HIV care for numerous patients with social problems.
Depression has been associated with reduced adherence to cART [21], reduced virological suppression [22] and increased mortality [7] in HIV-infected patients. The association between detectable viral load and occurrence of a psychiatric event may be explained by the fact that the latter may have been preceded by periods of psychiatric impairment (for example, depressive symptoms), which may have resulted in decreased adherence and virological failure.

These results underline the major role that socio-behavioural variables play in determining the incidence of severe/life-threatening psychiatric disorders and, more generally, in the prognosis of HIV-infection as a chronic disease. They emphasize the importance of comprehensive disease evaluation during cART follow-up. Interventions targeting the improvement of social conditions and mental health should be routinely associated with the medical treatment of HIV infection.

Our study may have some limitations. Importantly, the incidence rate of D/S/SA is lower than in the general population. The two possible main reasons for this are: firstly, only severe events requiring hospitalization or leading to life-threatening conditions were identified; secondly, depression may have been associated with a higher likelihood of dropping out, so the number of depressed patients (and probably of severe events) may have been underestimated. Nevertheless, as access to cART is free of charge in France, no potential selection bias should have affected the external validity of the results.

Most studies conducted in this field are cross-sectional. This is, as far as we know, the first longitudinal study to describe the occurrence of severe psychiatric events over

Table 2. Factors associated with the occurrence of the first depression/suicide/suicide attempt event among HIV-infected patients on combination antiretroviral therapy in the ANRS CO8 APROCO-COPILOTE cohort using univariate and multivariate Cox proportional hazard models

<table>
<thead>
<tr>
<th>Factor</th>
<th>Descriptive statistics</th>
<th>Univariate analyses</th>
<th>Multivariate analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Sociodemographic and psychosocial characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender, %</td>
<td>22.3</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Mean age at M0, years (so)</td>
<td>37.6 (9.5)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Being employed, %</td>
<td>54.9</td>
<td>0.24 (0.09, 0.60)</td>
<td>0.002</td>
</tr>
<tr>
<td>Strong social support from steady partner, %</td>
<td>46.1</td>
<td>0.54 (0.23, 1.25)</td>
<td>0.153</td>
</tr>
<tr>
<td>Alcohol consumption &gt;2(3) IU/day for women (men)</td>
<td>25.7</td>
<td>1.83 (0.79, 4.25)</td>
<td>0.160</td>
</tr>
<tr>
<td>Tobacco consumption &gt;20 cigarettes/day, %</td>
<td>17.2</td>
<td>2.86 (1.25, 6.56)</td>
<td>0.013</td>
</tr>
<tr>
<td>Stable housing, %</td>
<td>79.5</td>
<td>0.37 (0.16, 0.88)</td>
<td>0.024</td>
</tr>
<tr>
<td>Satisfaction with medical team’s explanations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None/little/some (reference), %</td>
<td>10.3</td>
<td>1</td>
<td>0.158</td>
</tr>
<tr>
<td>Quite a lot, %</td>
<td>41.6</td>
<td>0.24 (0.03, 1.73)</td>
<td></td>
</tr>
<tr>
<td>A great deal, %</td>
<td>43.9</td>
<td>1.73 (0.40, 7.52)</td>
<td>0.466</td>
</tr>
<tr>
<td>Physical quality of life comparable with the general population at M0, %</td>
<td>51.3</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Mental quality of life comparable with the general population at M0, %</td>
<td>42.6</td>
<td>0.47 (0.19, 1.15)</td>
<td>0.098</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean CD4+ T-cell count, cells/mm³ (so)</td>
<td>367 (214)</td>
<td>0.99 (0.99, 1.00)</td>
<td>0.041</td>
</tr>
<tr>
<td>Undetectable HIV RNA, %</td>
<td>44.9</td>
<td>0.23 (0.10, 0.56)</td>
<td>0.001</td>
</tr>
<tr>
<td>Adherence category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30% (reference), %</td>
<td>11.2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Between 80% and 99%, %</td>
<td>24.8</td>
<td>0.34 (0.11, 1.08)</td>
<td>0.067</td>
</tr>
<tr>
<td>100%, %</td>
<td>62.1</td>
<td>0.22 (0.08, 0.65)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

n=1,095 patients. The following fixed variable characteristics were not eligible for multivariate analysis (P-value >0.20 in univariate analysis): having a secondary-school certificate at baseline (M0), HIV transmission category, antiretroviral naivety at M0, time since first antiretroviral therapy prescription at M0, time since first HIV-positive test at M0, CDC clinical stage at M0 and HCV infection at M0. The following time-varying characteristics were not eligible for multivariate analysis (P-value >0.20 in univariate analysis): having children, taking psychotropic drugs, intravenous drug use during the previous 6 months, smoking cessation since last visit, quality of physician–patient relationship and confidence in one’s physician. Multivariate model is adjusted for gender, age and a mental quality of life at M0 comparable with that of the general population. *Descriptive statistics are computed either at M0 for fixed variables or at month 1 (M1) for time-varying variables. Fixed variable. †Time-varying variable. 

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a long follow-up and which attempts to identify both the associated pattern of correlates and potential risk factors.

It is true that the events we observe are probably only ‘the tip of the iceberg’. Even though it is difficult to ‘translate’ these events, defined according to the ANRS grading system into a detailed DSM-V diagnosis, we think that our results underline a clinically important problem in HIV-infected patients receiving cART. We hope that this analysis, despite its limitations, will help other researchers both to better explore this issue with more adequately designed studies and to assess the effectiveness of interventions to prevent such serious events.

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Disclosure statement

The authors declare no competing interests.

Additional file


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