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TITLE PAGE

Tobacco addiction and HIV infection: towards the implementation of cessation programs.

ANRS CO3 Aquitaine Cohort~~, 2004~~.

Antoine Bénard[1,2], Fabrice Bonnet[1,3], Jean-François Tessier[1], Hélène Fossoux[4], Michel Dupon[5], Patrick Mercié[1,6], Jean-Marie Ragnaud[5], Jean-François Viallard[7], François Dabis[1,2], Geneviève Chêne[1,2] and the Groupe d'Epidémiologie Clinique du Sida en Aquitaine (GECSA).

[1] INSERM, U593, Bordeaux, F-33076 France ; Université Victor Segalen Bordeaux 2, ISPED, Bordeaux, F-33076 France ;

[2] CHU Bordeaux, Bordeaux, F-33076 France ;

[3] CHU Bordeaux, Service de Médecine Interne et Maladies Infectieuses, Hôpital Saint-André, Bordeaux, F-33076 France ;

[4] CHU Bordeaux, Service de Maladies Respiratoires, Unité de Prévention et d'Aide au Sevrage Tabagique, Bordeaux, F-33076 France ;

[5] CHU Bordeaux, Fédération de Maladies Infectieuses et Tropicales, Hôpital Pellegrin, Bordeaux, F-33076 France ;

[6] CHU Bordeaux, Service de Médecine Interne, Hôpital Saint-André, Bordeaux, F-33076 France ;

[7] CHU Bordeaux, Service de médecine interne (A), Hôpital Haut-Lévèque, Bordeaux, F-33076 France.

Running Head : HIV infection and tobacco cessation programs

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Correspondence and request for reprints :

Geneviève Chêne, MD, PhD

INSERM U593 – ISPED - Case 11

Université Victor Segalen Bordeaux 2

146 Rue Léo Saignat 33076 Bordeaux Cedex. France

Tel : +33 557 571 257 - Fax : +33 557 571 172

E-Mail : genevieve.chene@isped.u-bordeaux2.fr

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ABSTRACT (262 Words, #250)

In treated HIV-infected patients, mortality is now dominated by non-AIDS-related causes in which tobacco smoking is a predominant risk factor. The implementation of tobacco smoking cessation programs is therefore warranted to increase survival but should consider the specificities of this population to be successful.

A cross-sectional survey within the ANRS CO3 Aquitaine Cohort of HIV-infected patients. All outpatients consulting in May-June 2004 were asked to complete a self-administered questionnaire including questions about tobacco and other drugs consumption, the Fagerström Test for Nicotine Dependence (FTND), a visual scale to estimate motivation to stop smoking and the Center for Epidemiologic Studies Depression (CES-D) scale.

Among 509 patients included, 74% were men, 41% were infected through homo or bisexual contact, 19% through injecting drug use and mean age was 44 years. Among the 257 (51%) ~~were~~ regular smokers (at least one cigarette/day), 60% had a medium or strong nicotine dependency, 40% were motivated to quit smoking and 70% had already tried at least once. A nicotine dependency (FTND ≥5) was more frequently reported in the 146 smokers (62%) with depressive symptoms (CES-D scale ≥17 (men) or ≥23 (women)) as compared to other smokers (70% versus 48%). 55 regular smokers (23%) were co-dependent to cannabis and 31 (12%) to alcohol. Overall, only 35 (14%) regular smokers were motivated, non co-dependent, without depressive symptoms and could be proposed a standard tobacco cessation program.

Depressive symptoms were highly prevalent in this ~~representative~~ population of HIV-infected patients. To be successful, smoking cessation interventions should be specifically built to take into account depression and co-dependencies in addition to nicotine dependence and motivation.

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Keywords: HIV Infections, Tobacco Use Disorders, Depressive Disorder, Motivation, Tobacco Use Cessation

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INTRODUCTION

When treated with combination Antiretroviral Therapy (cART), the Human Immunodeficiency Virus (HIV) infection is now considered as a chronic disease and current prognosis results from interactions between the disease itself, treatments and host specificities like co-morbidities and addictions. Indeed, over the past ten years, the proportion of death causes related to non-AIDS defining malignancies (especially lung cancer), non-AIDS bacterial infections and cardio-vascular diseases has currently reached 25 to 30 percent of all deaths among HIV-infected patients. [1-3] These disease conditions have at least one important modifiable risk factor in common: tobacco smoking. [4,5] The prevalence of tobacco smoking among HIV-infected patients is usually reported at higher levels than in the general population, as shown in a previous study of the Aquitaine Cohort or in the international D:A:D collaboration. [6,7] Nowadays, tobacco consumption is considered as the most important risk factor of cardiovascular diseases in this population. [8-10]

Tobacco smoking cessation has well known benefits on mortality and morbidity in the general population where tobacco cessation assistance programs are increasingly implemented. [4] These strategies are based on knowledge regarding nicotine and other dependencies, depression and motivation to quit smoking. These factors are indeed directly associated with success of a tobacco cessation attempt. [11] If some studies have already explored tobacco smoking behaviour among HIV-infected patients, [12-14] so far, data combining these factors to prepare specific interventions are missing in the field of HIV infection.

Our objective was to describe tobacco consumption among HIV-infected patients under care and to identify motivation, depression and dependencies among smokers to define appropriate interventions and prepare their implementation.

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METHODS

Design and study population

We conducted a cross-sectional survey from May 11th to June 11th 2004, enrolling all HIV-infected outpatients of the ANRS CO3 Aquitaine Cohort attending the participating clinics during the study period. This cohort includes all HIV-infected in- or outpatients of the participating clinic wards of the Bordeaux University Hospital and five other public hospitals in Aquitaine, south-western France, since 1985. [15] All patients included in the ANRS CO3 Aquitaine Cohort have given informed consent. The study was approved by the institutional review board of the Agence Nationale de Recherches sur le Sida et les Hépatites Virales (ANRS). Patients were asked to complete a self-administered questionnaire including: questions about tobacco, cannabis, alcohol and other drugs consumption, the Fagertröm Test for Nicotine Dependence (FTND), [16] a visual scale to estimate motivation to stop smoking and the Centre for Epidemiologic Studies Depression (CES-D) scale. [17]

The questionnaire was distributed to all outpatients, whether they were smokers or not, before or after their clinic visit. In order to ensure confidentiality, each questionnaire was distributed in a self-closing envelope identifiable only by the unique identification number of the patient in the cohort. To evaluate the exhaustivity of data collection, the outpatients register was compared daily to the list of responders.

Data collection and coding

According to the World Health Organisation recommendations, regular tobacco smokers were defined as consumers of one or more cigarette a day for at least one year. Occasional smokers were defined as consumers of less than one cigarette a day since at least one year. [18] Former smokers had a history of regular smoking.

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A FTND score ≥5 defined a moderate to strong nicotine dependency, that would require a substitutive treatment in case of tobacco smoking cessation according to the French Guidelines. [11]

A score ≥17 for men and ≥23 for women at the CES-D scale defined the presence of depressive symptoms, according to its adaptation to the French population. [19] Among the 20 items of the CES-D scale with values from 0 to 3, we chose to impute each missing value at 3. If, after imputation, the result of the score was under the threshold, we concluded to the absence of depressive symptoms. In all other cases, the CES-D score was considered missing.

The motivation to stop smoking was evaluated using a visual numeric scale, graduated from 0 (absolutely not motivated to stop smoking) to 10 (extremely motivated to stop smoking), routinely used by tobaccologists. [20] For a value ≥6, the patients were considered as significantly motivated to stop smoking and so have to be oriented to a ward tobacco cessation program.

Excessive consumption of other drugs than tobacco were defined according to the frequency of their consumption. Excessive alcohol consumption was defined as ≥2 glasses of alcohol/day for women and ≥3 for men. [21] Excessive cannabis consumption was defined as a daily consumption. Excessive consumption of morphine, barbiturates, benzodiazepines, amphetamines, ecstasy or lysergic acid diethylamide (LSD) was defined as at least a once day-consumption. Excessive consumption of heroine or cocaine was defined as at least a once week-consumption and excessive consumption of crack was defined as a consumption of at least once a month.

Results of nicotine dependency, depression and motivation to stop smoking were stratified on age (dichotomised at its median), gender, excessive drug consumption and history of tobacco cessation attempt that are known to be associated with tobacco smoking behaviour, and on other characteristics such as HIV transmission categories, duration since first HIV positive

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serology (dichotomised at its median) control of HIV infection (CD4 cell count < and ≥350/mm^3) and antiretroviral treatment that could potentially be associated with tobacco smoking behaviour.

We drew an outline of specific interventions using observed data on motivation, excessive drug consumption, depressive symptoms and nicotine dependency. Motivation, which is considered as the basis for smoking cessation, was the first step of the outline. Excessive drug consumption, which necessitates to be taken in charge before smoking cessation, was the second step. Depressive symptoms, which does not counter indicate smoking cessation intervention but needs to be treated to enhance the effectiveness of intervention, was the third step, and nicotine dependency was the fourth step.

Statistical methods

Sample size calculation

We anticipated that the proportion of regular smokers with a FTND score ≥5 would be 40%. Taking into account the feasibility of the recruitment, we calculated that the inclusion of 600 outpatients in the monthly period of the survey would allow for a precision of less than ±6%. Type one error was fixed at 5% (two sided) and the proportion of regular smokers among the overall sample at 50%.

Statistical analysis

Prevalence estimates are reported as proportions with their 95% confidence interval (CI). Differences of prevalence according to different patients characteristics were compared using Pearson's χ^2 test. Two multivariate logistic regression models were constructed to identify covariates of nicotine dependency and motivation to stop smoking. Statistical analysis used

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SAS software, version 8.2 (SAS Institute Inc., Cary, North Carolina, USA). A *p*-value <0.05 was considered as statistically significant.

RESULTS

Study profile

Six hundred and twenty one outpatients had a clinic visit in one of the five participating wards during the study period. Among them, 584 received a self-administered questionnaire and 509 completed it, yielding an exhaustivity of 82% ~~(fig. 1)~~.

Mean age of the respondents was 44 years and 74% were men. Two hundred and nine patients (41%) were infected through homo or bisexual contact, 160 (31%) through heterosexual intercourse, 94 (19%) through injecting drug use and 46 (9%) through other or unknown circumstances. The median duration since first HIV positive serology was 10 years and CD4 cell count was above 350/mm^3 in 358 patients (67%). Four hundred and forty four patients (81%) received cART, and CD4 cell count was above 350/mm^3 in 272 of them (66%).

The 112 non responders did not differ significantly from the 509 responders with respect to age (45 years in average), gender (63% were men), HIV transmission categories (36% heterosexual, 31% homo-bisexual and 21% injecting drug user), duration since first HIV positive serology (10 years), CD4 cell count (66% above 350/mm^3) or prevalence of regular tobacco smoking (46%).

Description of the study sample

Tobacco and other drug consumption

Among the 509 patients surveyed, 257 (51%) were regular smokers, 28 (5%) were occasional smokers, 119 (23%) former smokers and 105 (21%) non smokers. Mean age at smoking initiation was 15.4 years among regular smokers, 17.5 years among occasional smokers and

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15.9 years among former smokers. Mean number of years smoked was 23.9 among regular smokers, 24.6 among occasional smokers and 29.3 among former smokers.

Among former smokers, mean duration since last quit attempt was 8.8 years. Seventy nine (67%) former smokers did quit smoking after they had been diagnosed HIV-infected. Furthermore, 41 (34%) had stopped smoking for <6 months.

Excessive cannabis consumption was reported among 60 patients (13%) and was significantly associated with tobacco smoking status: 55 regular smokers (23%) were excessive cannabis consumers versus two (8%) among occasional smokers and three (2%) among former and non smokers ($p<0.001$).

Excessive alcohol consumption was reported by 41 individuals (8%). The proportion of excessive alcohol consumers was higher among regular smokers (n=31, 12%) than among occasional smokers (n=1, 4%) and former and non smokers (n=9, 4%) ($p=0.01$).

Depressive symptoms

Among the 464 individuals with a CES-D score available for analysis, 232 (50%) suffered from depressive symptoms (table 1). The prevalence of depressive symptoms was significantly higher among regular and occasional smokers (62% and 58%, respectively) than among former and non smokers (32% and 40%, respectively) ($p<0.001$). It was also significantly higher among individuals aged <45 years compared with older ones (54% versus 44%). Differences in prevalence of depressive symptoms were also observed between patients who had been diagnosed for their HIV infection for ≥10 years as compared with those diagnosed earlier (55% versus 43%), among excessive cannabis consumers versus non excessive consumers (72% versus 47%) and among injecting drug users as compared with other HIV transmission categories (67% versus 47%). The prevalence of depressive symptoms was not associated with gender, CD4 cell count or cART. It tended to be higher

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among excessive alcohol drinkers as compared to other patients (63% versus 45%, respectively) but this difference did not reach statistical significance (p=0.09) (table 1).

Description of regular smokers

History of tobacco consumption

The average number of cigarettes smoked per day among regular smokers was 15.7. Seven patients (3%) started regular tobacco consumption after they had been diagnosed HIV-infected. One hundred and seventy six regular smokers (70%) had already tried to quit smoking at least once, and this occurred after HIV was diagnosed among 109 (42%) of them. Median duration since the last quitting attempt was 1.9 years (inter-quartile range 0.6 to 5.9).

Dependency to nicotine

Fifty two regular smokers (22%) were not dependent to nicotine (FTND score ≤2) and 43 (18%) reported a low dependency (FTND score 3 or 4). One hundred and forty four regular smokers (60%) presented with a medium or strong nicotine dependency (FTND score ≥5) and, thus, would have required a nicotinic substitution in case of tobacco withdrawal. FTND score was missing for 19 individuals. The proportion of patients with a medium or strong nicotine dependency was significantly higher among regular smokers presenting with depressive symptoms compared to those without (70% versus 48% respectively, Odds Ratio = 2.46, p=0.002) (table 2). The proportion of regular smokers with a medium or strong nicotine dependency tended to be lower among patients treated with cART compared with those not treated with cART (57% versus 73%) but this difference did not reach statistical significance (p=0.07). We did not observe any nicotine dependency difference between patients treated with Protease Inhibitors compared with those without (59% versus 60%, p=0.87), between patients treated with Nucleosidic Reverse Transcriptase Inhibitors compared with those

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without (58% versus 68%, p=0.21) and between patients treated with Non Nucleosidic Reverse Transcriptase Inhibitors compared with those without (54% versus 62%, p=0.23).

Nicotine dependency was not associated with gender, age, duration since first HIV positive serology, HIV transmission categories, control of HIV infection, excessive cannabis consumption, excessive alcohol consumption, motivation to stop smoking or history of tobacco cessation attempt.

Due to an interaction between HIV transmission categories and excessive cannabis consumption, HIV transmission categories were not included in the multivariable analysis. The multivariate model showed the same results as the univariate analysis (table 2).

Motivation to quit smoking

One hundred and three regular smokers (40%) were considered motivated to stop smoking (motivation scale ≥6) and, on these grounds, could have been oriented toward a tobacco cessation program.

In the univariate analysis as in the multivariate analysis, the proportion of regular smokers motivated to stop smoking was significantly associated with history of tobacco cessation attempt. Fifty percent of the patients who have already tried to quit smoking showed a motivation ≥6 compared to 21% among those who have never tried to stop tobacco consumption (Odds Ratio = 3.9, p<0.001 in the multivariate model) (table 3).

In the univariate analysis, the proportion of regular smokers motivated to stop smoking tended to be lower among excessive cannabis or alcohol consumers compared with non excessive consumers (33% versus 45% and 27% versus 45%, respectively) but these differences did not reach statistical significance (p=0.13 and p=0.06, respectively). The difference of motivation between excessive and non excessive cannabis consumers was not retrieved in the multivariate analysis (Odds Ratio=1.2, p=0.64).

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In the univariate analysis as in the multivariate analysis, the proportion of regular smokers motivated to stop smoking did not vary according to gender, age, duration since first HIV positive serology, HIV transmission categories, CD4 cell count, cART, presence of depressive symptoms or excessive alcohol consumption (*p*-values >0.2 for all comparisons).

Outline of specific interventions

All the 257 regular smokers included in our survey could have benefited from an intervention. But, based on our findings on motivation, excessive cannabis or alcohol consumption, depressive symptoms and dependence to nicotine, four categories can be identified to draw an outline of specific interventions to help them to stop smoking (fig. 2). Only 14% were motivated, non co-dependent, without depressive symptoms and could be entered in a classical tobacco cessation program, 12% were motivated and not co-dependent, had depressive symptoms or nicotine dependency and were in need of a smoking cessation program taking depression into account, 12% were motivated but co-dependent to other drugs which was a priority in the case management, 56% were not motivated to stop smoking and needed to receive information to first increase motivation.

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DISCUSSION

Our study provides up-to-date and in-depth results on motivation to stop smoking, nicotine dependency, depression and other drugs addictions in a large cohort of French HIV-infected patients. The observed prevalence of regular tobacco smoking (51%) confirms the results reported in previous studies, including in this cohort. [6,7,12,14] Furthermore, data on the history of tobacco consumption showed that 70% of the regular smokers surveyed had already tried to quit smoking at least once, and for 42% after their HIV diagnosis. These results are consistent with those found in previous studies. [12-14] We found that history of tobacco cessation attempt was associated with a higher motivation to quit smoking. This finding is consistent with the transtheoritical model in which the probability of change increases with the number of change attempt. [22]

An important proportion of regular smokers (42%) were motivated enough to benefit from behavioural support or medication but a substitution would have often been required in case of tobacco withdrawal. We reported that a significant proportion of regular smokers was excessive cannabis or alcohol consumer (23% and 12%, respectively). We showed that a large majority of regular smokers had a medium or strong nicotine dependency and would therefore need a nicotinic substitution in case of tobacco withdrawal. The high prevalence of depressive symptoms observed among regular smokers confirms the results already found in the general population, [23,24] and this underlines the importance of depression management in the tobacco cessation process among HIV-infected patients.

We acknowledge two potential limitations to our study. Firstly, we only included out-patients and our study population could thus be considered as not totally representative of HIV-infected individuals. However, our survey has been conducted to evaluate the possibility of

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implementing a cessation program in this population, and if such a program is launched, it will be specifically dedicated to out-patients. Secondly, if the thresholds we chose for the FTND score and the CES-D scale are validated and routinely used, it is not the case for the evaluation of the motivation to stop smoking. However, the numeric scale we used was chosen for its simplicity, rapidity and easiness of interpretation and is routinely used by tobaccologists in the context of clinical practice. [20]

HIV-infected regular smokers showed a high degree of motivation to quit smoking and a large majority had already tried to quit smoking. However, the prevalence of tobacco consumption remains high, certainly due to difficulties to stop tobacco consumption encountered by HIV-infected smokers. Several factors reported in our study could explain this situation.

The HIV disease itself, affecting the quality of life, may act as a limiting factor. It is likely though that tobacco consumption could represent a coping strategy against health discomfort, economic difficulties and/or the lack of social support. [25-27] Precarious social conditions, that have been found to be associated with smoking status in HIV-infected patients, [12] can also represent a limitation to quit smoking, regardless of the mode of acquisition of HIV although we could not investigate these characteristics.

The frequency of excessive cannabis or alcohol consumers among regular smokers was high. Excessive alcohol and cannabis consumption has been found to be associated with a lower readiness to quit smoking in populations not known as HIV-infected [28] as well as among HIV-infected individuals. [12,13] It has to be diagnosed and treated prior to a tobacco cessation attempt [11]. Nicotine dependency, that was found to be high among HIV-infected regular smokers, is also known to be a limiting factor of success of tobacco cessation. Many smokers find it difficult to quit because they have become addicted to the nicotine present in the smoke. [11,29] Treatment of nicotine dependency must therefore be the base of any tobacco

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cessation intervention. Finally, depressive symptoms are known to increase the risk of tobacco cessation failure. [30] The observed prevalence of depressive symptoms among HIV-infected regular smokers was high. We also found that it was associated with a higher nicotine dependency and a higher cannabis consumption. Therefore, we believe that depressive symptoms may indeed represent one of the major issues for tobacco cessation among HIV-infected patients.

The outline of specific interventions we elaborated showed that less than 1/6 of HIV-infected regular smokers were motivated, non excessive consumers of other drugs, without depressive symptoms and could be proposed a standard tobacco cessation program. HIV-infected smokers need behavioural support and medication in order to stop tobacco consumption. We provide evidence for clinicians that tobacco cessation interventions among HIV-infected patients are relevant and must be based on interdisciplinary collaboration. HIV-infected regular smokers can be dispatched in three main categories: those who could benefit from standard tobacco cessation programs, with a management of depressive symptoms if needed, those who need a treatment of co-dependencies prior to smoking cessation and those who first need motivational interventions. Our study provides sufficient information to now set up and evaluate tobacco cessation programs among HIV-infected patients.

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COMPETING INTEREST STATEMENT

Antoine Bénard: No conflict

Fabrice Bonnet: No conflict

Jean-François Tessier: No conflict

Hélène Fossoux: No conflict

Michel Dupon: No conflict

Patrick Mercié: No conflict

Jean-Marie Ragnaud: No conflict

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ETHICS COMMITTEE APPROVAL

All patients included in the study have given informed consent. The study was approved by the institutional review board of the Agence Nationale de Recherches sur le Sida et les Hépatites Virales (ANRS, http://www.anrs.fr).

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TABLES LEGEND

Table 1. Characteristics associated with depressive symptoms in a population of HIV-infected individuals, ANRS CO 3 Aquitaine Cohort, 2004

Table 2. Characteristics associated with dependency to nicotine among HIV-infected regular smokers (N=257), ANRS CO 3 Aquitaine Cohort, 2004

Table 3. Characteristics associated with motivation to stop smoking among HIV-infected regular smokers (N=257), ANRS CO 3 Aquitaine Cohort, 2004

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FIGURE LEGENDS

~~**Figure 1. Tobacco addiction in the ANRS CO3 Aquitaine Cohort, 2004. Study profile**~~

Figure 1. Possible strategies to help regular smokers stop smoking according to motivation, depressive symptoms and dependence to nicotine and other drugs. ANRS CO3 Aquitaine Cohort, 2004.

(Percentages are calculated from the 257 regular smokers).