Influence of substance use and cognitive impairment on adherence to antiretroviral therapy in HIV+ patients

Influencia del consumo de sustancias y el deterioro cognitivo en la adherencia al tratamiento antirretroviral en pacientes VIH+

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Abstract

Strict adherence to antiretroviral treatment (ART) is needed to ensure the effectiveness of HIV treatment. The adverse effects of substance abuse and neurocognitive impairment on medication adherence have both been suggested by several studies. Therefore, the aim of this research is to study the relationship among adherence to ART, cognitive dysfunction, and abuse of certain substances (alcohol, heroin, cocaine, other stimulants, cannabis and benzodiazepines) and/or methadone treatment in our social environment. We performed an observational case-control study with a sample of 125 HIV+ patients, who were classified as patients with poor adherence (cases) and subjects with adequate compliance (controls). Adherence was defined by the Hospital Pharmacy and verified with the Simplified Medication Adherence Questionnaire (SMAQ) and the reference physician's clinical impression. Cognitive functioning was measured with the Zoo Map Test and Trail Making Test (TMT). Substance abuse was collected through a semi-structured clinical interview protocol. Statistical analysis was made using a binary logistic regression model. The results indicate that both alcohol abuse and neurocognitive impairment measured by Zoo Map Test were significantly associated with poorer adherence to ART. No significant association was found between adherence and other substance use, or between adherence and TMT score. Screening of cognitive impairment measured by the Zoo Map Test and alcohol abuse may lead to the development of strategies to improve de adherence to ART in HIV+ patients.
Keywords: HIV; Antiretroviral therapy; Medication adherence; Cognitive dysfunction; Substance use.

Resumen

La adherencia estricta al tratamiento antirretroviral (TAR) es imprescindible para que este sea eficaz en la disminución de la morbimortalidad asociada al VIH. Se ha sugerido que el consumo de sustancias y el deterioro cognitivo constituyen factores de riesgo para una mala adherencia. En este sentido, el objetivo de este estudio es evaluar cuál es la influencia sobre la adherencia al TAR de la disfunción cognitiva, así como del consumo de determinadas sustancias (alcohol, heroína, cocaína, otros estimulantes, cannabis y benzodizepinas) y/o el tratamiento con metadona, en el marco concreto de una población española de referencia. Se realizó un estudio observacional tipo casos y controles con una muestra de 125 pacientes VIH+, que se dividieron en sujetos malos adherentes (casos) y buenos adherentes al TAR (controles). La adherencia se evaluó mediante el reporte de Farmacia Hospitalaria, contrastada con la escala Simplified Medication Adherence Questionnaire (SMAQ) y la opinión del profesional médico de referencia. La función cognitiva fue evaluada con el Test del Mapa del Zoo y el Trail Making Test (TMT), y el consumo de sustancias, mediante un protocolo de historia clínica semi-estructurada. El análisis estadístico se realizó mediante regresión logística binaria. Los resultados mostraron que el abuso de alcohol y el deterioro en la función cognitiva ejecutiva, medida por el Test del Mapa del Zoo, constituyen factores de riesgo independientes para una mala adherencia. No se ha demostrado relación de la adherencia al TAR con el consumo de otras sustancias ni con la puntuación obtenida en el TMT. La detección de deterioro cognitivo mediante el Test del Mapa del Zoo, así como del consumo de alcohol, podrían ayudar a desarrollar estrategias de mejora del cumplimiento terapéutico en pacientes VIH+.
Palabras clave: VIH; Tratamiento antirretroviral; Adherencia terapéutica; Deterioro cognitivo; Consumo de sustancias.

Introduction

Human Immunodeficiency Virus (HIV) belongs to the Retroviridae family and is the cause of the Acquired Immunodeficiency Syndrome (AIDS), which constitutes a worldwide public health problem of the greatest magnitude (Fauci & Lane, 2005). The establishment of treatment regimes consisting of the combination of antiretroviral drugs has allowed us to slow down the progression of HIV. Therefore, antiretroviral treatment (ART) has implied an important decrease in mortality and morbidity associated with HIV, and, in many cases, it turns an infection that used to be invariably lethal into a chronic disease (Lovejoy & Suhr, 2009; Tran, Nguyen, Nguyen, Hoang & Hwang, 2013). Nevertheless, to obtain a complete clinical and virological response, and prevent the onset of resistant viral strains, strict compliance to treatment is necessary, among other factors. The majority of authors defend that in order to ensure the efficacy of ART, compliance must be above 90-95%. However, maintaining such a high compliance can be difficult for many patients (Ingersoll, 2004; Lovejoy & Suhr, 2009).

In recent years, there has been an attempt to clarify the factors can have an impact on adherence to ART, in order to identify potentially modifiable risk factors and develop strategies to improve the therapeutic plans (Thaler, Sayegh, Kim, Castellon & Hinkin, 2015; Tran et al., 2013). It has been suggested that the following factors may be associated with poorer compliance: low socioeconomic level (Peltzer & Pengpid, 2013; Tsuyuki & Surratt, 2015), the presence of treatment side effects, patients' lack of perceived efficacy, emotional stress, the absence of social and family support, the complexity of the treatment regimen (Ammassari et al., 2002), youth, and cognitive impairment (Thaler et al., 2015). In addition, it has been proposed that poorer compliance is related to presence of psychopathology, mainly depressive (Ammassari et al., 2004), certain personality traits (Hutton & Treisman, 2008), and substance consumption (Azar et al., 2015). Nevertheless, there are few studies in this regard in our sociocultural context, so we believe that it is necessary to investigate the aforementioned associations in the Spanish population.

HIV is a neurotropic virus that invades the central nervous system (CNS) at an early stage, producing neurotoxicity, neuroinflammation, and neurodegeneration. The pernicious effect in the CNS can occur through the direct action of the virus, or indirectly by means of immunosuppression, which can affect the CNS in the form of opportunistic infections and malignancies: cryptococcosis, toxoplasmosis, progressive multifocal leukoencephalopathy, primary lymphoma of the brain, etc. (Bragança & Palha, 2011; Group of experts from the "Grupo de Estudio de Sida" (GeSIDA; in English AIDS Research Group) and the Secretariat of the "Plan Nacional sobre el Sida" (SPNS; National AIDS Plan, 2014). Prior to the introduction of ART, a great number of patients developed severe cognitive impairment in the last stage of the disease, called *HIV associated dementia* (HAD) by the American Neurology Association in 1991. This was differentiated from another entity that did not meet the criteria of dementia, but in which there were slight alterations that interfered with daily life: *Minor cognitive motor alteration* (MCMA). In recent years, HAD is increasingly rare; however, it has been found that a percentage of long-term patients presents cognitive impairment, some even with the infection systematically well controlled (Cysique & Brew, 2009; GeSIDA & SPNS, 2014; Solomon & Halkitis, 2008). With the progress of the disease, there is often a decline in the executive function, motor functioning, attention, memory, and processing speed, and some behavioral changes, such as apathy and lethargy, also appear (Anand, Springer, Copenhaver & Altice, 2010; Andrade et al., 2013, Vázquez-Justo, Vergara-Morague, Piñón-Blanco, Guillén-Gestoso & Pérez-García, 2016). Antinori et al. (2007) conducted a nosological review of the cognitive alterations associated with HIV ("Frascati criteria"), included in the term *HIV associated neurocognitive disorders* (HAND). The new classification proposed divides this entity into three categories: *asymptomatic neurocognitive impairment* (ANI), *mild neurocognitive disorder* (MND), and *HIV associated dementia* (HAD). The first two are characterized by the development of a mild impairment in at least two neurocognitive domains, without meeting the criteria for dementia, and without interference or with mild interference, respectively, in the individual's habitual functioning. In HIV associated dementia, there is marked impairment and interference in daily life (Antinori et al., 2007; GeSIDA & SPNS, 2014).

In recent years, numerous studies have reported that this cognitive impairment is another factor related to poorer adherence to ART (Andrade et al., 2013; Hinkin et al., 2004; Lovejoy & Suhr, 2009). Diminished cognitive functioning may condition the presence of "forgetfulness", which is the most frequent reason for missed doses of medication in the treatment (Ammassari et al., 2004; Blackstone, Woods, Weber, Grant & Moore, 2013; Hinkin et al., 2002). Other authors have proposed that poor adherence to ART determines a worse cognitive evolution, as it accelerates the progression of the disease (Cysique & Brew, 2009; Waldrop-Valverde et al., 2006). Nevertheless, it is plausible to consider that this may actually be a bi-directional relationship (Andrade et al., 2013; Hinkin et al., 2004; Lovejoy & Suhr, 2009). It must be taken into account that ART usually involves a complex treatment regimen, which implies mechanisms related to planning and decision-making, and therefore requires a notable cognitive demand. In this case, the cognitive deficit has to be taken into account in the design of the treatment, in order to establish an adequate regime for each patient's characteristics (Blackstone et al., 2013; Hinkin et al., 2002; Solomon & Halkitis, 2008). There

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is no uniformity in the literature regarding which cognitive areas have greater influence on adherence to ART. According to the available evidence, poorer adherence could be associated with deficits in the executive functions, the learning capacity, attention, the working memory, the prospective memory, and processing speed. Nevertheless, the results of the diverse studies are heterogeneous, and the mechanisms underlying this relation have not been clarified (Ammassari et al., 2004; Andrade et al., 2013; Lovejoy & Suhr, 2009). Knowing which cognitive areas are determinant to adherence would allow us to implement strategies to counterbalance failures due to cognitive dysfunction (Altice, Kamarulzaman, Soriano, Schechter & Friedland, 2010; Blackstone et al., 2013; Hinkin et al., 2002).

Substance use disorder has a very high prevalence in HIV+ patients, in whom it is especially problematic for several reasons: it is associated directly and indirectly with an increase in the transmission of the virus and with a worsening of the immune status, regardless of treatment-related factors, and with a increase in morbidity and mortality in general, as well as with poorer adherence to ART (Altice et al., 2010; Parsons, Starks, Millar, Boonrai & Marcotte, 2014). The substances that have proven to be risk factors for poor adherence are mainly, although not exclusively, alcohol, cannabis, cocaine, amphetamines, and heroin. However, the results regarding this association are not homogeneous in all the studies (Altice et al., 2010; Waldrop-Valverde et al., 2006). Whereas there is a fairly extensive consensus about the negative influence on adherence to ART of alcohol consumption (Azar, Springer, Meyer & Altice, 2010; Gonzalez, Barinas & O'Cleirigh, 2011), and cocaine consumption (Meade, Conn, Skalski & Safren, 2011; Rosen et al., 2013), the results are disparate for substances like cannabis (González-Álvarez, Madoz-Gúrpide, Parro-Torres, Hernández-Huerta & Ochoa Mangado, 2019; Lovejoy & Suhr, 2009). Concerning opioids, the consumption of heroin has been associated with poorer adherence (Azar et al., 2015). There are contradictory results about the influence on adherence found in a program of maintenance with methadone (PMM) in users of drugs by parenteral route (Azar et al., 2015; Cohn et al., 2011). In patients who consume multiple substances, it has been suggested that the combination of alcohol and cannabis could be more negative for adherence than the exclusive use of alcohol, and, in turn, the combination of alcohol and cocaine could be associated with the worst results in adherence (Parsons et al., 2014). The type of substance and the consumption patterns could be influential factors in this association. Different mechanisms have been proposed that could sustain this association: a chaotic lifestyle with unstable time schedules (Hinkin et al., 2007; Ingersoll, 2004), an increase in forgetting to take medication (Anand et al., 2010; Ingersoll, 2004), the failure to control impulses and disinhibition favored by consumption (Anand et al., 2010;

Hinkin et al., 2007). In addition, some patients voluntarily omit their medication during periods of consumption, as they believe it is incompatible with treatment (Gonzalez et al., 2011; Kalichman et al., 2015).

However, the chronic consumption of substances can imply an increase in the risk of early cognitive impairment (Altice et al., 2010; Anand et al., 2010; Vázquez-Justo et al., 2016). Individuals taking opioids show deficits in attention, memory, and executive function both during their active use and in early abstinence. Moreover, it has been suggested that dependence on opioids worsens the neurocognitive disorders associated with HIV because they foment viral replication by means of a direct negative effect on the immune system. This effect is even more evident in combination with cocaine (Anand et al., 2010). There is a greater cognitive dysfunction and poorer therapeutic adherence in active consumers of cocaine compared to abstainers. It has been suggested that cognitive impairment partially moderates the association between cocaine consumption and adherence to ART (Gonzalez et al., 2011; Meade et al., 2011). With regard to alcohol, its dependence may cause persistent brain damage, subcortical atrophy, and hypometabolism in frontal lobes. Moreover, a synergistic pernicious effect of alcohol consumption and infection by HIV on the CNS has been described, as the cognitive impairment associated with chronic consumption of alcohol is greater in HIV+ individuals than in HIV- individuals (Anand et al., 2010). All this seems to suggest that there is an interrelationship between cognitive impairment, adherence to ART, and substance consumption (Anand et al., 2010; Hinkin et al., 2007).

The present work aims to analyze the relation between substance consumption and cognitive function in the adherence to ART in HIV+ patients. Although there is international literature in this respect, references of the impact of substance consumption and cognitive dysfunction in the adherence to ART are limited in the assistential environment of the Spanish population (González-Álvarez et al., 2019; Ortego, Huedo-Medina, Vejo & Llorca, 2011). The hypothesis of this study is that substance consumption and cognitive impairment can negatively influence adherence to ART in HIV+ patients.

Methodology

Area and population of study

A total of 125 patients were included in this study. Prior to the present article, preliminary data from a subset of these individuals were reported in another publication of our work group (González-Álvarez et al., 2019). In the aforementioned article, we studied the relation between adherence to ART and alcohol consumption, associated or not with the use of other substances; in this work, we also introduce the study of the cognitive component.

The inclusion criteria were: age between 18 and 65 years, diagnosis of HIV infection, being in regular follow-up in the Service of Infectious Diseases of the University Hospital Ramón y Cajal of Madrid, having initiated ART at least one year before the assessment, and that this treatment was dispensed only through the Hospital Pharmacy Service of this hospital. Regular follow-up was considered as having attended at least two scheduled visits in the past year (Tripathi, Youmans, Gibson & Duffus, 2011).

Exclusion criteria were: acute active infectious processes, active cancer processes, discrepancies in the classification of the patients as good or bad adherents between the different classification methods used, and the report of a rate of adherence between 90% and the 95%. Adherence to ART was assessed by means of the percentage of treatment withdrawn during the year prior to the assessment, according to the report of the Hospital Pharmacy. This data was verified by means of the questionnaire Simplified Medication Adherence Questionnaire (SMAQ), an instrument to assess adherence to treatment, validated for use in HIV+ patients (Knobel et al., 2002). Based on both parameters, we classified the patients as good or poor adherents, and we informed their respective reference physicians of the Department of Infectious Diseases of the group to which each patient had been assigned. If there was any inconsistency between adherence reported by the Hospital Pharmacy and the outcome of the SMAQ, or if the reference professional's clinical impression disagreed with the outcome of the classification of the two aforementioned methods, the patients were excluded. As there is no consensus about the minimum effective adherence (Viswanathan et al., 2015), we chose the most conservative minimum and maximum limits, in order to increase the power of classification of the method. For this reason, we excluded from the study those patients in whom adherence between 90% and 95% was reported.

All the patients included in the study were informed, accepted participation, and signed the informed consent. The study was approved by the Ethics Committee of Research Clinic of the University Hospital Ramón y Cajal.

Type and general Design of the study

This is of an observational, cross-sectional case-control study. Patients were assigned to each group as a function of adherence to ART. Patients with poor adherence to ART were considered "cases", defined according to the report of the Hospital Pharmacy as those patients who had picked up less than 90% of the ART doses during the past year. Patients of the same provenance, who, at the time of entering the study differed only in their good adherence to ART, were considered the "controls", defined as those who had withdrawn more than 95% of their ART doses during the past year (Paterson et al., 2000).

Procedure of the sample selection:

The selection of cases was carried out by consecutive sampling of a list of non-adhering patients generated ordinarily and with monthly frequency by the Hospital Pharmacy. The controls were selected by consecutive sampling of the list of patients who had an appointment in the monographic consultation of HIV of the Service of infectious Diseases. Sample selection took place between May 2013 and September 2015.

Data collection procedure:

Data collection was implemented according to a semi-structured clinical history protocol, specially designed for this research, which included the SMAQ scale. We also included in the protocol a battery of neuropsychological tests validated for Spanish population, among which were the Trail Making Test (TMT) and the Zoo Map Test.

- The Zoo Map Test is part of the neuropsychological exploration battery Behavioral Assessment of the Dysexecutive Syndrome (BADS). This tool is used especially to measure the skill of planning as part of the executive functions. Planning can be defined as the skill to organize behavior as a function of a specific goal that must be achieved by means of a series of intermediate steps. It has been suggested that it is a two-step process: formulation and execution. Formulation is the mental ability to develop a logical mental strategy guiding the course of action, while execution is the competence to carry out the plan developed in the formulation (Oosterman, Wijers, & Kessels, 2013).

- The Trail Making Test (TMT) is one of the most widely disseminated and used instruments in neuropsychological evaluations seeking to measure processing speed and executive function. Diverse studies agree that it has a complex structure that encompasses various cognitive mechanisms. Visual search, perceptual/motor speed, processing speed, working memory and general intelligence are some of the constructs most frequently cited that are thought to contribute to test performance. It consists of two parts: part A mainly examines visuo-perceptive skills, and part B mainly involves the working memory and secondarily, flexibility to switch tasks (Sánchez-Cubillo et al., 2009).

Definition of the variables of the study

Sociodemographic variables, such as age, sex, race, civil status, socioeconomic level, educational level, and work status were collected. In order to increase the statistical power of the analysis, some variables were recoded, preserving their clinical meaning. The categories of absence of profession, home-keeper, student, and unskilled worker were considered as unqualified profession; skilled workers with occupational qualification, employees, civil servants, and liberal professions were classified as qualified workers.

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With regard to the sociodemographic level, the accumulation of debts, being unable to deal with payments, or the need for external aid to the family unit were considered as economic risk.

In addition, we included variables of HIV infection and its treatment: co-infection with Hepatitis C Virus (HCV), time in follow-up, time in treatment with ART, number of doses of medication a day, number of pills a day, and presence a supervisor of the treatment, among others. The history of substance consumption in the 12 months prior to assessment (alcohol, cocaine, heroin, cannabis, stimulants and benzodiazepine, as well as treatment with methadone) was described. We categorized alcohol consumption as harmful consumption or non-problematic consumption, as a function of the criteria of the tenth Review of the International Classification of Diseases (World Health Organization [WHO], 1992). For the remaining substances, we classified as positive any consumption pattern, although all individuals who admitted consumption presented at least weekly frequency. We also included the presence of risk behaviors associated with substance use by parenteral route: sharing and reusing syringes. Regarding the neuropsychological tests, in the Zoo Map Test, we collected the main variable Total Score and four secondary variables: Number of Hits, Number of Errors, Planning Time, and Total Test Performance Time. We defined the variables TMT-A score and TMT-B score: in both cases, the score was obtained directly as a function of the time spent to complete the task.

Statistical analysis

Firstly, we conducted a raw analysis of the results. By means of the Kolmogorov-Smirnov test and the viewing of the graphs, the quantitative variables were observed to follow a normal distribution. In the cases of discrepancy, we followed the graphic information. With regard to the descriptive analysis, in the variables that followed a normal distribution, the results are expressed as means and standard deviations. For the nonparametric variables, we used the median and the interquartile range (IQR) between 25% and 75%. For the qualitative variables, the descriptive statistic was the percentage. The comparison of cases and controls was carried out through Pearson's chi-square in the qualitative variables. For the quantitative variables that followed a normal distribution, we used Student's t-statistic for independent samples, and for those in which at least one of the groups followed a non-normal distribution, we used the Mann Whitney-U statistic

Lastly, stepwise multivariate binary logistic regression analysis was performed (odds ratio). Initially, we included variables that had been shown to be related to adherence to ART in the raw analysis, and that also met the criterion of biological plausibility, and were related to the object of our study. We also included variables that had been shown to be interesting in the prior literature. The following variables were included in the multivariate analysis: age, gender, socioeconomic level, educational level, number of pills prescribed per day, risk behaviors with regard to sharing syringes, supervision of mediation by third parties, co-infection with VHC, substance consumption (alcohol, cannabis, cocaine, heroin, and treatment with methadone), and psychometric test scores (Zoo Test and TMT-B).

Data with a p-value < 0.05 were considered significant.

Results

Results of the descriptive analysis and of the raw analysis

General description of the sample and comparative analysis of the sociodemographic and clinical variables. We analyzed a total sample 125 subjects, 79 controls and 46 cases. Of these, 68% were males, and 84% were Caucasian. The median of age of the sample was 48.4 years (IQR: 43.6 – 52.8).

No statistically significant differences were observed between cases and controls with regard to the variables sex, age, race and civil status. The absence of significant group differences in the variable age excludes age as a possible confounding factor in relation to cognitive impairment. A significant difference was found in academic level, as the frequency of higher studies was greater in the controls (p = .001). In addition, the cases had lower professional qualification (p = .027), and worse socioeconomic level (p < .001). Both academic and the socioeconomic level were included in the multivariate analysis in order to study the hypothesis of our study regardless of the possible influence of these heterogeneous variables between cases and controls. Occupational qualification was not included due to its lower statistical significance and to the need to limit the number of variables included in the multivariate analysis in proportion to our sample size. No differences were found between cases and controls for the variables time in treatment, time in follow-up, and number of doses of medication per day. There was a statistically significant difference in the number of pills that made up the daily treatment between the two groups, which was higher in the cases (p = .002). The greater need for supervision of ART by third parties was significant in the cases (p = .001) (Tables 1 and 2).

Co-infection with HCV was significantly greater in the group of the cases (70.5% compared to 34.6% of the controls, p < .001). In addition, the cases presented more risk behaviors of sharing syringes (58.7% versus 26.6%, respectively, p < .001).

Comparative analysis of variables related to substance consumption in the past year. Concerning substance consumption, 67.4% of the cases and 30.4% of the controls presented illegal substance consumption in the past year, and this difference was statistically significant (p < .001). Problematic consumption of alcohol was higher in the cases (p < .001). Likewise, consumption of cocaine (p = .001), other stimu-

Table 1. *Comparative analysis of sociodemographic variables.*

		Control subjects n (%)	Cases n (%)	X^2 p
Sex	Male	52 (65.8%)	33 (71.7%)	0.494
	Female	27 (34.2%)	13 (28.3%)	
Race	Caucasian	70 (88.6%)	35 (76.1%)	0.066
	Other	9 (11.4%)	11 (23.9%)	
Marital status	Living with partner	28 (35.4%)	18 (39.1%)	0.680
	Other	51 (64.6%)	28 (60.9%)	
Academic level	Primary/Graduate	32 (40.5%)	33 (71.7%)	**0.001**
	High School/VT*/University	47 (59.5%)	13 (28.3%)	
Profession	Unqualified	31 (40.3%)	28 (60.9%)	**0.027**
	Qualified	46 (59.7%)	18 (39.1%)	
Socioeconomic level	No economic problems	69 (87.3%)	21 (45.7%)	**‹0.001**
	Economic risk	10 (12.7%)	25 (54.3%)	
Supervision of treatment	Never	71 (89.9%)	30 (65.2%)	**0.001**
	Sometimes/always	8 (10.1%)	16 (34.8%)	

Note. *VT: Vocational training.

Table 2. *Comparative analysis of clinical variables.*

	Control subjects Median (IQR¥)	Cases Median (IQR¥)	Mann-Whitney U p
Age (years)	49.1 (45.3 – 53.4)	46.4 (6.3)*	0.079
Time in follow-up (years)	15.0 (8.0 – 21.0)	18.0 (9.0 – 22.0)	0.125
Time in treatment (years)	13.0 (5.0 – 19.0)	16.5 (8.0 – 20.0)	0.176
Number of pills/ day	2.0 (1.0 – 3.0)	3.0 (2.7 – 4.0)	**0.002**
Number of doses/day	1.0 (1.0 – 2.0)	1.0 (1.0 – 2.0)	0.866

Note. ¥Interquartile range (IQR 25 – IQR 75); *Mean (Standard deviation).

Table 3. *Comparative analysis of variables related to substance consumption in the past year.*

	Control subjects n (%)	Cases n (%)	X^2 p
Any illegal substance	24 (30.4%)	31 (67.4%)	**‹0.001**
Alcohol (problematic)	12 (15.2%)	22 (47.8%)	**‹0.001**
Cannabis	24 (30.4%)	19 (41.3%)	0.215
Cocaine	14 (17.7%)	21 (45.7%)	**0.001**
Other stimulants	0 (0%)	3 (6.5%)	**0.022**
Heroin	3 (3.8%)	7 (15.2%)	**0.023**
Treatment with methadone	5 (6.3%)	16 (34.8%)	**‹0.001**
Benzodiazepines	2 (2.5%)	10 (21.7%)	**‹0.001**

lants (p = .022), and heroin (p = .023) was also more frequent among the cases. The number of subjects who were in PMM for opiate addiction was significantly greater in the cases (p < .001). Also benzodiazepine abuse was statistically more frequent among the cases (p < .001). No significant differences were found with regard to the consumption of cannabis (Table 3).

Comparative analysis of variables related to the neuropsychological tests. In the Zoo Map Test, significant differences between cases and controls were found in four of the five variables included in our correction, with the controls always scoring higher: in Total Score (p = .002), Number of Hits (p = .045), Number of Errors (p = .014), and Total Test Performance Time (p = .038). With regard to the TMT, in both parts, the cases needed significantly more time to complete the tests than the controls (TMT-A: p = 0.003 and TMT-B: p = .001) (Table 4).

Adjusted analysis of variables related to adherence to ART. Logistic Regression

Of the 125 subjects of the total sample, 111 (88.8%) were included in the adjusted analysis . Of these, 74 were controls and 37 were cases. Due to missing some of the data that were introduced in the analysis —specifically, the score in TMT-B and/or the total score in the Zoo Map— 14 subjects were lost. The reason is that these patients dropped out of the interview prior to its completion, possibly due to fatigue and the prolonged duration of the interview. We estimated models of multiple imputation of the missing values, which did not show relevant changes or significant improvement of the final model; for this reason, we decided to assume the missing values.

The final model correctly classified 82.9% of the global sample, with more specificity than sensitivity (Hosmer & Lemeshow's test: 90.5% of the controls and 67.6% of the cases), and it explained 53.4% of the variable of adherence.

Table 5 presents the variables that showed a statistically significant relation with adherence to ART.

Sociodemographic and clinical data. According to the results obtained, the risk of poor adherence increases in the following cases: being younger, being male, low socioeconomic level, an ART guideline consisting of a higher number of pills per day, and HCV co-infection. In our model, the high-risk behavior of sharing syringes, the need for supervision of treatment, and the patient's educational level were not shown to be associated with poor adherence.

Substance consumption. Harmful consumption of alcohol increased the risk of being classified as a poor adherent by 3.398 (95% CI [1,040, 11,100]) versus the situation of abstinence or non-problematic consumption, after controlling for the variables identified in Table 5. However, the consumption of cannabis, cocaine, or heroin and the thera-

peutic use of methadone were not significantly associated with a worsening of therapeutic adherence.

Neuropsychological tests. The total score obtained on the Zoo Map, after controlling for the variables identified in Table 5, was significantly related to adherence to ART. Each additional point in the score of this test multiplies by 0.659 the probability of being considered a poor adherent. Inversely, each additional point multiplies by 1.517 (95% CI [1.149, 2.000]) the probability of being considered good adherent. However, no statistically significant relation between the score obtained in the TMT-B and adherence was found.

Discussion

The goal of the present study is to study whether substance consumption and cognitive impairment, evaluated by means of the Zoo Map Test and the TMT, negatively influence adherence to ART in HIV+ patients. The results obtained confirm partially our working hypothesis.

The differences between cases and controls in the performance of the neuropsychological tests were significant for almost all of the variables of interest. In the raw analysis of the Zoo Map Test, differences were observed in four of the five variables. No significant difference between cases and controls was found in the variable planning time, although the total performance time was significantly higher in poor adherents. This may be due to the fact that the cases usually began the task impulsively and overestimated their capacity to solve it, and then, they needed more time to complete the test and they committed more errors. Of the neuropsychological variables introduced in the multivariate analysis (TMT-B and total score on the Zoo Map), the latter was the only one that maintained the statistically significant association with adherence to ART in the final logistic regression model, after controlling for the rest of variables. The ART is a complex regimen whose adequate adherence requires skills of planning and performance; therefore, it is logical that a difficulty to plan, as measured by the Zoo Map Test, will lead to a poorer capacity to adhe-

Table 4. *Comparative analysis of the variables related to neuropsychological tests.*

		Control subjects Median (IQR¥)	Cases Median (IQR¥)	Mann-Whitney U p
Trial Making Test	TMT-A (seconds)	41.0 (34.0 − 54.0)	53.5 (39.5 − 74.2)	**0.003**
	TMT-B (seconds)	85.0 (67.0 − 124.5)	143.0 (86.0 − 200.0)	**0.001**
Zoo Map Test	Nr. of hits	8.0 (7.0 − 8.0)	7.0 (7.0 − 8.0)	**0.045**
	Nr. of errors	1.0 (0.0 − 1.0)	1.0 (0.0 − 3.0)	**0.014**
	Total score	7.0 (6.0 − 8.0)	5.0 (3.5 − 5.0)	**0.002**
	Planning time (seconds)	75.0 (39.0 − 146.0)	70.0 (22.5 − 121.0)	0.205
	Total performance time (seconds)	145.0 (89.0 − 203.5)	187.5 (126.0 − 240.0)	**0.038**

Note. ¥Interquartile range (IQR 25 − IQR 75).

Table 5. *Logistic regression, "Enter" method.*

	B	Stand. error	Wald	Degrees of freedom	p	Exp(B)	95% CI for Exp(B)
Age	-0.110	0.046	5.852	1	**0.016**	0.896	0.819 − 0.979
Sex	-1.338	0.655	4.173	1	**0.041**	0.262	0.073 − 0.947
Number of pills	0.514	0.211	5.938	1	**0.015**	1.672	1.106 − 2.528
Socioeconomic level	1.296	0.637	4.136	1	**0.042**	3.654	1.048 − 12.737
HCV co-infection	1.821	0.662	7.563	1	**0.006**	6.178	1.687 − 22.620
Alcohol	1.223	0.604	4.103	1	**0.043**	3.398	1.040 − 11.100
Total Zoo Map score	-0.417	0.142	8.662	1	**0.003**	0.659	0.500 − 0.870
Constant	-0.463	2.497	0.034	1	0.853	0.630	

re to this regimen. These results are congruent with those found in other studies, in which a significant association has been shown between a disturbance in executive functions and poorer adherence to ART (Andrade et al., 2013; Waldrop-Valverde et al., 2006).

It is also significant that the cases obtained worse scores than the controls in the performance of both versions of the TMT in the raw analysis. This supports the results obtained in previous studies that relate a deficit in working memory, analyzed by means of the TMT, with poorer adherence to ART (Wagner, 2002). Nevertheless, there is more support in the literature for the association between adherence to ART and the B version of the TMT (Solomon & Halkitis, 2008; Thaler et al., 2015). Due to the need introduce a proportionate number of variables to our sample size, we decided not to include the A version of the TMT in the multivariate analysis. Even so, the TMT-B showed no statistical significance in the final model, possibly because there is an overlap between the areas evaluated by the Zoo Map Test and the TMT-B.

The association between alcohol consumption and poorer adherence is maintained in our logistic regression model after controlling for other consumptions, such that alcohol is a risk factor for poor adherence, regardless of the use of other substances. According to the results of the raw analysis, the consumption of heroin, cocaine, and other stimulants is significantly higher in poor adherents but the association is not maintained in the multivariate model. This latter finding contrasts with the results obtained in other studies: Azar et al. (2015) found a significant relation between poorer adherence and the use of intravenous cocaine and heroin, independently; and Rosen et al. (2013) suggest a negative effect of the consumption of alcohol, heroin, cocaine, and other stimulants on adherence. The absence of such a relation in our study may be due to the scarce number of subjects who reported these consumptions, that patients with more severe consumptions are not represented in our sample, or that there is an overlap between alcohol consumption and these substances. No significant difference was found in the consumption of cannabis between cases and controls, which supports the results of previous studies (Rosen et al., 2013; Slawson et al., 2015). Regarding the PMM programs in users of drugs by parenteral route, they are statistically more frequent in poor adherents in the raw analysis, but this association was nonsignificant in the multivariate analysis. This finding differs from those suggested by other authors (Malta, Strathdee, Magnanini & Bastos, 2008), which might due to the fact that the profile of patients in PMM in our sample correlates with a worse socioeconomic level and clinical situation, which is congruent with the findings of other studies (Martínez-Luna et al., 2018; Pedrero-Pérez & Grupo MethaQoL, 2017).

The results show that HCV co-infection was significantly more frequent among the patients with poor adherence. This variable has not been shown to influence adherence to ART in other prior studies (Shuper et al., 2016). HCV co-infection may be associated with factors that hinder adherence: higher presence of hepatotoxicity, lower efficacy of ART, more prevalence of substance consumption, poorer cognitive performance, and greater social marginalization. Nevertheless, this possible relation is beyond the scope of our work, and other more specific studies are needed to determine it. The patients with the worst socioeconomic level are more likely to be poor adherents in the multivariate analysis, a finding that coincides with prior studies (Tsuyuki & Surratt, 2015). As already suggested by other authors (Nachega et al., 2014), in our study, ART regimes consisting of a greater number of pills are related to worse adherence. Nevertheless, this situation may be influenced by feedback, such that a worse immune status, related to poorer adherence and to resistances developed in that context, would require a more complex treatment regime, which, in turn, would hinder adherence even more. However, there is no difference between the number of daily doses, which probably reflects the professionals' effort to simplify the treatment regimes, in spite of the fact that cases require a greater number of pills a day.

From the data obtained in our work, it follows that harmful alcohol consumption and poorer cognitive executive functioning, as measured by the Zoo Map Test, are significantly related to poor adherence to ART. This finding corroborates a large part of the results published in the international literature within Spanish population (Andrade et al., 2013; Azar et al., 2010; Thaler et al., 2015). With regard to Spain, in the meta-analysis carried out by Ortego et al. (2011), a relation between poor adherence and consumption of alcohol and other substances was found, but only in the univariate model; cognitive impairment was not studied. In the prior study carried out by our group (González-Álvarez et al., 2019), it was found that harmful alcohol consumption is a risk factor for poor adherence to ART, independently of the consumption of other substances.

Part of the limitations of the study may be related to the provenance of the sample: an external consultation of the Infectious Diseases Service of a hospital that is a center of reference for the treatment of the HIV. Due to the assistential context, this may have been an aged population, with a high average follow-up and treatment time, which would have excluded more severe cases with a greater difficulty to maintain a regular follow-up in the consultation. However, although small, the loss of subjects in the multivariate analysis may have led to an exclusion bias of the more deteriorated profiles, which may present more difficulties to complete the tests.

The instruments employed in this work to study cognitive impairment specifically measure the executive functions.

In this sense, another possible limitation could be not having expanded the exploration to other cognitive domains.

With regard to substance consumption, we did not use any method to corroborate the criteria of abuse/dependence or substance consumption disorder; we only registered, through the interview with the patient, the presence or absence of consumption in the past year, and we did not perform screening tests of biological samples. However, the prevalence of consumption of heroin, cocaine, and other stimulants was scarce in the sample, which may have limited the capacity to assess the real effect of these variables on adherence. There may also be a bias concerning patients with more severe consumption patterns, who may have been excluded for not meeting the criterion of a regular outpatient follow-up. Hence, the results can only be extrapolated to a population with a similar profile. We recommend studying the impact of cognitive impairment and substance consumption on adherence to ART in populations characterized by more severe consumptions, greater psychosocial deterioration, and less access to health resources, to determine the nature of this association in patients with that profile.

Another possible limitation is that the method of quantifying adherence by the Hospital Pharmacy Service is based on the patients' withdrawal of the medication, not strictly on its consumption. Therefore, defects in the schedule of doses, duplicity of doses, or the loss of medication would be biased in the data collection. Nevertheless, a possible strength of the study is this count is confirmed by means of two complementary methods: the SMAQ instrument and the opinion of the professional in charge. This design could decrease the risk of overestimating adherence and increase the probability of a correct classification of the patients (Henegar et al., 2015).

The importance of adequate adherence to ART has been extensively described as a means to reduce the morbidity and mortality associated with HIV (Lovejoy & Suhr, 2009; Thaler et al., 2015). Patients with cognitive dysfunction, as well as those who problematically consume illegal substances and/or alcohol are at greater risk of being poor adherents. As already suggested in the prior literature, these variables act as independent risk factors, whose combined effects are summed for poor adherence (Moore et al., 2012; Thaler et al., 2015). Nevertheless, the present study does not allow us to elucidate the mechanisms underlying this association. Cognitive impairment may be a partial mediator between substance consumption and adherence to ART, as has been suggested in previous studies (Gonzalez et al., 2011; Meade et al., 2011). It would be necessary to carry out studies with larger samples and a different design to propose more specific hypotheses in this regard.

On the one hand, it is essential to inquire about the existence and pattern of substance consumption in order to establish measures to decrease its influence and to facilitate access to therapeutic resources (Gonzalez et al., 2011;

Parsons et al., 2014). However, it is necessary to detect cognitive impairment in the habitual clinical practice, but there is currently no specific neuropsychological battery for HIV+ patients (GeSIDA & SPNS, 2014; Muñoz-Moreno et al., 2014). In this sense, the TMT-B and the Zoo Map Test can be useful screening tools that are easy to apply (GeSIDA & SPNS, 2014; Oosterman et al., 2013; Sánchez-Cubillo et al., 2009). Prior studies have shown that more complex treatment regimes are related to poorer adherence, particularly in individuals with cognitive deficits (Hinkin et al., 2002). In patients who score positive in the screening of impairment of cognitive functions, simplification of the treatment regime might promote better adherence. In addition, cognitive stimulation strategies, motivational work, and the use of devices of environmental support (alarms, lists, involvement of relatives or third persons…), among others, have been suggested as potentially beneficial strategies in these patients (Bragança & Palha, 2011; Parsons et al., 2014; Tran et al., 2013).

To conclude, the study shows the importance of cognitive dysfunction and alcohol consumption, after controlling for the rest of the variables, as independent risk factors of poor adherence to ART. However, sociodemographic and clinical variables, such as the male sex, youth, low socioeconomic level, co-infection with HCV, or a large number of pills per day are also associated with worse adherence. The relevance of these results in the clinical practice lies in the importance of expanding our knowledge of the factors that modulate adherence to ART, in order to implement primary and secondary prevention strategies.

Intervention on the modifiable risk factors is necessary in order to minimize therapeutic noncompliance in HIV patients. The screening and the detection of substance consumption could help to implement measures to promote access to specific treatment facilities. In addition, the systematic detection of deficits in cognitive functioning would allow us to establish strategies to improve treatment adherence. The improvement of therapeutic adherence, in turn, constitutes a preventive measure for the development of cognitive impairment and helps to decrease the morbidity and mortality associated with HIV.

Conflict of interest

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