Drug Use and Antiretroviral Adherence in Methadone Maintenance Patients: A Longitudinal Study

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ABSTRACT

This study investigates the relationship between antiretroviral treatment and drug abuse. For this prospective study, investigators followed a sample of 100 HIV+ patients on a methadone maintenance program in Madrid (Spain), over a period of time of one year. A high percentage of participants (more than 50% according to the indicators) were seen to be compliers, another percentage continued without taking the drug, and from 12% to 18% of the participants discontinued or started the treatment. All of these groups were statistically associated with different drug abuse patterns, measured both through self-reports and urinalyses. The first group usually remained abstinent, the second used opiates, cocaine, benzodiazepines and alcohol, those who discontinued the treatment had relapsed and consumed opiates, cocaine and had increased their frequency of alcohol consumption, and those starting the treatment had given up the use of opiates and cocaine and reduced alcohol intake. The use of alcohol, opiates and cocaine were the variables best discriminating amongst the groups.
Key words: HIV, methadone program, compliance, drug abuse, alcohol abuse.

RESUMEN

En el presente trabajo se estudia la relación entre la adherencia a los tratamientos antirretrovirales y el consumo de drogas. El estudio, de corte prospectivo, sigue durante un año a una muestra de 100 pacientes VIH+ en un programa de mantenimiento con metadona en Madrid (España). Los resultados mostraron que un alto porcentaje de sujetos (más del 50% según los indicadores) permanecieron adherentes, que otro porcentaje siguió sin tomar la medicación y hubo entre un 12% y un 18% de sujetos que abandonaron el tratamiento o lo iniciaron. Todas estos grupos se asociaron estadísticamente a distintos consumos de drogas, medidos tanto a través de autoinforme como de muestras de orina. Los primeros solían permanecer abstinentes, los segundos consumían heroína, cocaína, benzodiacepinas y alcohol, mientras que los que abandonaron el tratamiento habían recaído en el consumo de opiáceos, cocaína y habían aumentado la frecuencia de consumo de alcohol, y los que iniciaron tratamiento habían abandonado el consumo de opiáceos, cocaína y reducido el consumo de alcohol. El consumo de alcohol, de cocaína y opiáceos fueron las variables que mejor discriminaron entre los grupos.
Palabras clave: VIH, programa de metadona, adherencia, abuso drogas, abuso alcohol.

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Since the current treatment for HIV-AIDS involves the combination of several drugs, with strict dosage schedules, for an indefinite time period along with added side effects, this makes it more likely that patients do not comply with such treatment. In fact, one of the main threats faced for the treatment of AIDS in Western countries is related to the lack of treatment compliance (Jensen-Fangel, 2004).

Patients with HIV-AIDS and a history of drug abuse show lower compliance rates than other infected patients and are less likely to have started any type of antiretroviral treatment (Mocroft, Johnson, Lazzarin, *et al.*, 1999). The fact that they have been attributed a chaotic lifestyle and social problems such as legal problems, unemployment, or being homeless involves that they will have difficulties to maintain the adequate behavior required for compliance. This improves when the patients start treatment for opiate dependence, particularly in a methadone maintenance program (Gordillo, del Amo, Soriano, & González Lahoz, 1999; Riera, De La Fuente, Castanyer, *et al.*, 2002; Wood, Montaner, Braitstein, *et al.*, 2004). Therefore, the start of a detoxification program and the stability of the methadone programs are associated with the start of HIV treatment and with a positive prevention practice (Bouhnik, Carrieri, Rey, *et al.*, 2004; Gossop, Marsden, Stewart, & Treacy, 2002; Muga, Egea, Sanvisens, *et al.*, 2004), leading the survival prognosis to be consistent with that of other communities in the case of drug abstinence, but markedly worsening in the case of continuing drug abuse (Mocroft *et al.*, 1999). The improvement experienced by some patients included in the methadone treatment program reaches the point at which their condition of being under treatment does not distinguish compliers from non-compliers when the sample is taken from the general infected population (Palepu, Horton, Tibbetts, Meli, & Samet, 2004). However, the active use of illegal drugs or alcohol does involve a direct risk, regardless of whether or not they are on treatment (Hinkin, Hardy, Mason, *et al.*, 2004; Mohammed, Kieltyka, Richardson-Alston, *et al.*, 2004; Murphy, Marelich, Hoffman, & Steers, 2004).

The data on antiretroviral treatment compliance found in the literature are highly diverse and hardly comparable, as the time points tested are different (one or two days, weeks or one month) and because different criteria for an adequate compliance are followed (80%-95%), as well as various methods for measuring compliance, self-reports or drug blood concentration levels. Therefore, Moatti, Carrieri, Spire, *et al.* (2000) reported 34.8% of non-compliers (80%) in a sample of patients treated with buprenorphine, findings similar to those of Avants, Margolin, Warburton, Hawkins, and Shi (2001) in the phase of stabilisation of a methadone program considering a four-week interval (80%). In other cases, the values found are 34% drop-outs after detoxification on an inpatient basis (Muga *et al.*, 2004).

Although a lower compliance with antiretroviral drugs has been shown in HIV-AIDS participants on methadone programs, the factors affecting compliance are not so well-known. Initially, distinctions due to sexual differences were put forward with different predictive variables being associated (Haug, Sorensen, Lollo, Gruber, Delucchi, & Hall, 2005).

In some studies, age, alcohol and other drug abuses or the occurrence of adverse events in their lives are associated with reduced compliance (Moatti *et al.,* 2000); other cases include self-efficacy, social support, imprisonment and drug abuse (Kerr, Marshall,

Walsh, *et al.*, 2005), and others include viral burden, educational level reached, depression and emotional state (Avants, Margolin, Warburton, *et al.*, 2001). Adverse drug reactions and other factors such as memory loss and the use of drugs are mentioned as barriers to compliance in women (Powell-Cope, White, Henkelman, & Turner, 2003). To be noted is the study carried out by Bounhik *et al.* (2002), where predictive factors of compliance were evaluated in a sample of HIV+ patients with a past medical history of drug abuse. The conclusion was clarifying in that, among those who maintained an active drug use, this was the main factor related to compliance, while among those who continued drug abuse, social stability was the best predictive factor of compliance.

The relevance of other variables is also considered, such as anxiety, stress or depression (Gebo, Keruly, & Moore, 2003; Reynolds, Testa, Marc, *et al.*, 2003) included in some specific interventions designed to enhance compliance (Ballester, 2003; Smith, Rublein, Marcus, Brock, & Chesney, 2003), although patient self-efficacy and self-control are actually critical. These variables can also be associated with compliance (Chesney, 2003; Ladero, Orejudo, & Carrobles, 2005). In addition, depression has been shown to have an effect, independent from compliance, on the more advanced stages of the disease, leading to a more unfavourable disease outcome (Haubrich, Little, Currier, *et al.*, 1999).

Of all the above, the most established is obviously the relationship between drug abuse and non-compliance (Bouhnik, Preau, Vincent, *et al.*, 2005; Riera *et al.*, 2002; Witteveen & Van Ameijden, 2002), which has the greatest impact upon antiretroviral treatment. Those patients on treatment with methadone and who continue actively using one or more drugs also show compliance issues. Of these drugs, opiates and cocaine are particularly relevant, not missing the role of other legal psychotropic drugs such as benzodiazepines (Ladero, Orejudo, Carrobles, & Malo, 2005, Martini, Recchia, Nasta, *et al.*, 2004; Sharpe, Lee, Nakashima, Elam-Evans, & Fleming, 2004). A significant importance is attributed to alcohol, considered as a possible risk independent from other substances (Papelu, Horton, Tibbetts, Meli, & Samet; 2004; Gossop *et al.*, 2002) and a triggering factor for practices of risk of HIV (Stein, Charuvastra, Anderson, Sobota, & Friedman, 2002). The relevance of drug use is also shown in studies aimed at enhancing compliance through interventions combining motivational interviewing and cognitive behavioral therapy aimed at enhancing compliance with drug therapy as well as reducing substance use (Parsons, Rosof, Punzalan, & Di Maria, 2005).

To date, most studies on compliance have been carried out using cross-sectional and retrospective designs, longitudinal studies being less common or limited to short time periods in which the evolution of compliance is followed. However, this methodology involves certain limitations for establishing relationships between compliance and possible prospective variables. Besides this, the most common approaches for considering compliance are based on the number of tablets taken, or on compliers and non-compliers failure to understand the complexity associated to the situation (Spire, Duran, Souville, *et al.*, 2002), with different compliance patterns associated with various reasons, contexts, behaviors and social support levels (Hill, Kendall, & Fernández, 2003). The direct responsibility of the patients also involves taking the medication, something frequent, for example, in the decisions not to take HIV-AIDS treatment (Roberts & Mann, 2003).

Kerr *et al.* (2005) described that up to 44% of the 160 Canadian HIV-positive Injecting Drug Users (IDUs) gave up the treatment and drop-outs depended on variables related to self-efficacy and imprisonment.

The primary objective of this study is to analyze the evolution of drug abuse, as well as the pattern of compliance in a group of patients on a methadone maintenance program in Spain (MMT). This study is particularly relevant considering that in our country, unlike other European countries, the prevalence of HIV-AIDS cases in previous and current parenteral drug users is high (Bermúdez & Teva, 2004), and even when no differences have been found in disease progression in parenteral drug user patients following the Highly Active Antiretroviral Therapy (HAART) treatment throughout different European countries, the associated factors have been shown to change (van Asten, Zangerle, Hernández Aguado, *et al.*, 2005).

METHODS

Participants

The participants were selected from two of the *Integral Attention for Drug Abuse Centers* (IADAC, CAID in Spanish) of the Region of Madrid (henceforth CAM). Of the 250 patients of the Center of Torrejón de Ardoz, 83 participants were selected who met the inclusion criteria of the study (over 18 years of age, HIV-positive, taking part in the methadone maintenance program and being on antiretroviral medical prescription) and none of the exclusion criteria (not giving informed consent, not physically appear at the appointment with the investigator, be hospitalized, bed-ridden or in prison at the time of data collection). The sample was completed with 17 other participants from the IADAC at San Blas who also met the abovementioned criteria and who were selected at random, including in the sample those giving their consent as they come for collecting their dose of methadone on the given day.

The final sample consisted mainly of men (80%), of a low socio-economic level (71%), with elementary studies (92%) and employed (50%). The mean age was 37 years (ranging from 20 to 49) and 77% had been in prison. Most were in stages B (44%) and C (34%) of the disease, with an average viral burden of 25530 copies/ml, and 45% of participants with a viral burden below 50 copies/ml. Most (52%) had between 200 and 500 CD4, with an average of 398.67. All of them were prescribed antiretroviral drugs at some time during their lives. At the end of the study, the participants had been an average of 77.69 (SD: 24.81) months in the methadone program, with a maximum of 128 months and a minimum of 13. They had completed a total of 4.23 (SD: 3.25) treatment trials previously and had an average of 18.12 years (SD: 5.42) of heroin use, 15.80 (SD: 5.29) of cocaine use and 13.91 (SD: 6.40) of benzodiazepine use.

The policy of the methadone maintenance programs of both centers involves a low threshold, not requiring abstinence as a necessary condition to continue in the program. The program was started in 1995, so some subjects may be in the program since that date. Normalization is facilitated by home dosing (weekly and three times a

week), with daily collection only for patients starting the program. The users are offered the possibility to collect their doses at different dispensary points: at the center, at the Metabus (mobile methadone dispensation service of the CAM) or at certain agreed retail pharmacies. All users undergo a toxicological control, penalizing missing controls (one or two per week) with temporary loss of the home doses. The treatment team includes a physician, a social worker, an educator and a psychologist. Special attention is paid to the health condition of the participant, for which a psycho-educational intervention for HIV infected users is included.

During the follow up, only data from 91 people were collected. Of the rest, four had died and the remaining had moved to other centers.

Variables and instruments

The following variables were included in this study. Variables related to drug abuse and previous treatments:

- Time of opiate dependence (expressed in years), time of use of cocaine and time of use of benzodiazepines. The data for this variable were obtained from the medical records of each participant at baseline (Round 1).
- Time on the Methadone Maintenance Program (MMT), number of times under treatment for the drug addiction problem (previous to MMT), and time spent on the treatments previous to MMT (expressed in months). As in the above case, this information was obtained from the medical records of the participant (Round 1).
- Use of opiates, cocaine, cannabis, benzodiazepines, assessed by the presence of traces of these drugs in two urine samples from the participants. An indicator of multi-drug-use was obtained from the sum of the results of the urine sample for opiates, cocaine, and benzodiazepines (Round 1: $\alpha = .59$; Round 2: $\alpha = .55$). It does not include the sample for cannabis as it shows low communality with the rest in an exploratory factorial analysis. We shall call this variable *summation of the use of heroin, cocaine and benzodiazepines* (Rounds 1 and 2).
- After obtaining the data on drug use according to the urine indicator, the participants were classified according to their evolution throughout the year; thus we intended to analyze the percentage of participants that maintained compliance discontinuing their use of each drug considered, those who on the contrary continued their use, as well as the participants who had experienced some change, positive if they had discontinued drug abuse or negative if they had relapsed.
- Self-report of frequency of use of opiates, cocaine, cannabis, benzodiazepines and alcohol (Rounds 1 and 2). The levels considered (*abstinence, more than twice a month, more than once a week, more than twice a week, several times a day*) provided information about the frequency of drug use of the different drugs considered in the past month.
- As in the case of the objective measures of drug use, self-reported data were analyzed in an evolutionary manner, dividing the participants into those with increasing drug abuse and those decreasing it. The frequency of alcohol intake has been analyzed of the same way. The participants rated themselves as abstinent, continuing with daily use, and reducing or increasing the frequency of use.

Highly Active Antiretroviral Therapy (HAART) compliance variables:

- Self-reported compliance, with three timing criteria, *yesterday, last week and last month*. The values initially adopted ranged from full compliance, taking all tablets since the day before, every day of the week and month, to full non-compliance, with some intermediate degrees (*every day, nearly every day, some days, very few days and never*). The variable will be treated as dichotomous, with compliers defined as those participants who faultlessly completed their treatment.
- The longitudinal nature of the study will allow us to finally differentiate the various compliance levels, and above all, the evolution throughout the study. Therefore, there will be finally four groups: compliers who follow the treatment even after the year of the study (*remaining compliant for the previous day, the previous week and the previous month*); compliers who discontinued the treatment; previous non-compliers (Round 1) who started antiretroviral therapy (*starting treatment group*) and participants still failing to take the medication after the one year period (*continue without treatment group*).

Measures of compliance through self-reporting are common in compliance studies, and the time periods considered range from the day before, the past three days, the past week or the past month (Papelu *et al.*, 2004; Stein, Rich, Maksad, *et al.*, 2000). The measures of self-report of the day and of the week, as other objective measures of compliance, show a direct relationship with viral burden, and with its reduction after the treatment (Arnsten, Demas, Farzadegan, *et al.*, 2001).

Procedure

Data were collected during the months of April, May and June 2003 (Round 1) and the same months of the next year (Round 2). In order to carry out the study, the list of all users on the methadone maintenance program was reviewed, selecting HIV+ subjects. Their medical records were reviewed to check that at some time during their methadone treatment at the IADAC they had started an antiretroviral treatment, regardless of whether they continued or not.

The history of previous treatments, drug abuse and the frequency of visits to the Center were obtained from the participants' records at the Center. The results of the toxicology controls were completed once the toxicology department at the CAM provided them (approximately one week later).

Once these data were collected, an appointment was made with the interviewer and the characteristics of the study were explained to the subjects, asking them to participate. All of them should give their signed consent and during the interview they were administered the specific assessment questionnaire, which was designed *ad hoc* for this investigation. The tests were carried out by the interviewer with a duration of between 15 and 20 minutes, in order to prevent that the participants became tired.

Statistical Analysis

Once the groups described above were established, the relationship between degree of compliance and consumption variables, and degree of consumption change

were analyzed using contingency tables. However, for simplifying the presentation of the results, the percentages of drug use (urine screening test) and the measures of frequency (self-report) are given. The statistics used to measure the degree of association between variables were Pearson's Chi-square test and the Goodman-Kruskal tau test. Both tests provide information concerning the association between the nominal variables. The Goodman-Kruskal tau allows also for analyzing the relationship between the two variables under the hypothesis that one of them is the dependent (compliance) and the other the independent. In the case of the quantitative variables, the measurement differences according to each compliance group were analyzed by ANOVA tests (Pardo & Ruiz, 2005). We have dismissed performing multivariate analysis because of the low number of cases in some of the groups.

RESULTS

With regard to compliance with the antiretroviral treatment, at the beginning of the study (Round 1) 61% of the participants had taken the adequate medication the previous day, whereas one year later, 69% had done it. In Round 2, there were 8 cases with missing values. For the case of the previous week, 60% and 63.5%, respectively, had an adequate compliance and for the previous month the figures were 44% and 51.8%. The analysis of the changes evidenced that after one year 51.2%, 47.0% and 37.9% remained compliers, whereas 13.4%, 19.3% and up to 36.1% failed to take the medication adequately. From 12% to 17% of the participants had changed their condition for each category (Table 1).

With regard to drug abuse, 19% and 12.9% had traces of opiates in Rounds 1 and 2, respectively, 32.0% and 32.3% of cocaine and 52% and 59.8% of benzodiazepines, and 54% and 55.4% of cannabis. The use of opiates showed the best outcome, with a high percentage of abstinent participants, a small number of participants who continued drug abuse, a few relapsing, and a large number of drop-outs. For the rest of the drugs the outcome was worse, as the number of participants still consuming and the relapses were still high, though the number of subjects who quit was significant (Table 1).

Regarding multi-consumption, 36% of the cases yielded negative test results and other 36% gave positive results for one of the three drugs, 15% for two and 13% for the three. According to self-reports, consumption levels were very similar to those shown in the analytical samples.

Bi-variate Analysis. As shown in Tables 2, 3 and 4, the four groups of compliers, non-compliers and those changing their behavior in this area differed in drug abuse patterns at the study baseline (Round 1), particularly for opiates and cocaine. There were also differences in the use of benzodiazepines and alcohol. This was not the case for cannabis. The analysis of these associations, however, showed that the main difference among the groups of participants was seen between the participants who remained compliers and those who did not, because in Round 1 there were hardly any differences between those who changed and those who did not, even finding that those who gave up the medication evidenced abstinence and those who started the treatment evidenced consumption.

Table 1. Frequencies of adherence and drug use during year 2003, 2004 and changes between both years.

Adherence to HAART		
	2003	2004
Yesterday	61 (61.0%)	58 (69.0%)
Previous week	60 (60.0%)	54 (63.5%)
Previous month	44 (44.0%)	44 (51.8%)

Change adhesion to HAART 2003-04	Treatment drop out	Continue without treatment	Start the treatment	Remain adherent
Yesterday	15 (18.3%)	11 (13.4%)	14 (17.1%)	42 (51.2%)
Previous week	15 (18%)	16 (19.3%)	13 (15.7%)	39 (47%)
Previous month	10 (12%)	30 (36.1%)	14 (16.9%)	29 (34.9%)

DRUGS USE		
Drug (urine sample)	2003	2004
Opiate	19 (19.0%)	12 (12.9%)
Cocaine	32 (32.0%)	30 (32.3%)
Cannabis	52 (52.0%)	55 (59.8%)
Benzodiazepines	54 (54.0%)	51 (55.4%)

Changes in drug use (urine sample) 2003-04	Drug use decreases	Drug use continues	Drug use is stopped	Remain abstinent
Opiate	3 (3.2%)	9 (9.7%)	9 (9.7%)	72 (77.4%)
Cocaine	10 (10.75%)	20 (21,5%)	9 (9.7%)	54 (58%)
Cannabis	15 (16.12%)	40 (43%)	7 (7,5%)	30 (32.2%)
Benzodiazepines	11 (14.1%)	38 (41.3%)	11 (12.0%)	30 (32.6%)

Alcohol (Self-report)	2003	2004
Every day	34 (34.0%)	43 (47.3%)
Occasional	40 (40.0%)	24 (26.4%)
Never	26 (26.0%)	24 (262.4%)

Change in drug use (Self-report) 2003-04	Frequency increases	Maximum consumption (daily) continues	Consumption is reduced	Continued abstinence / occasional consumption
Alcohol	17.6%	53.8%	2.2%	26.4%

In line with the above, there were no differences amongst the groups in terms of history of drug consumption or previous treatments. In the case of the time of participation in the methadone program, a variance analysis of the four groups of compliance revealed some differences in the months taking part in this program (F (3.78)= 3.58, *p*= .017) reported for the previous day (Table 3), but the multiple Scheffé comparisons did not show differences amongst the groups (*p*> .05).

The data on drug abuse for Round 2 and the analysis of the changes from the previous data collection were much more significant and clarifying. The participants differed in their use of cocaine in Round 2, above all, and to a lesser degree in their use of benzodiazepines and alcohol (Tables 2, 3 and 4). The change in drug use added information to the importance of the evolution of opiate consumption.

Table 2. Adherence (Yesterday) by drug use (urine sample, self-report).

Adherence to HAART N	Abandon treatment 15	Continue treatment 11	Start treatment 14	Remain adherent 42	Total 82	χ^2
			YESTERDAY			
			Year 2003			
Opiates (urine sample)	33.3%	54.5%	35.7%	2.4%	20.7%	19.62***
Cocaine (urine sample))	33.3%	63.6%	50.0%	6.7%	31.7%	11.74**
Cannabis (urine sample)	26.7%	81.8%	57.1%	47.6%	50.0%	8.10*
BZD (urine sample)	40.0%	81.8%	78.6%	45.2%	54.9%	9.31*
Summation for OP-CC-BZD	1.06 (1.2)	2.00 (1.0)	1.64 (0.9)	.64 (0.7)	1.07 (1.0)	25.61***
Opiates (self-report)	0.86 (1.5)	1.72 (1.8)	0.78 (1.47)	.16 (0.6)	0.60 (1.3)	22.34*
Cocaine (self-report)	0.66 (1.29)	1.54 (1.4)	1.50 (1.7)	.42 (0.8)	0.80 (1.2)	21.97*
Cannabis (self-report)	1.20 (1.2)	3.09 (1.5)	3.28 (1.2)	1.85 (1.9)	2.14 (1.8)	21.24*
Benzodiazepines (self-report)	2.66 (1.2)	3.27 (1.1)	1.76 (1.6)	2.24 (1.6)	2.24 (1.6)	19.21
Alcohol (self-report)	0.86 (1.1)	2.36 (1.6)	2.28 (1.5)	1.35 (1.6)	1.56 (1.5)	14.75
			Year 2004			
Opiate (urine sample)	26.7%	27.3%	7.1%	7.1%	13.4%	5.983
Cocaine (urine sample)	46.7%	72.7%	28.6%	19.0%	32.9%	12.95**
Cannabis (urine sample)	53.3%	90.9%	64.3%	52.4%	59.8%	5.766
BZD (urine sample)	46.7%	81.8%	71.4%	47.6%	56.3%	6.058
Summation for OP-CC-BZD	1.20 (1.0)	1.81 (0.9)	1.07 (0.9)	.73 (0.8)	1.02 (.9)	13.07
Opiates (self-report)	.60 (1.2)	.72 (1.4)	.07 (.26)	.07 (.34)	0.25 (0.8)	20.329
Cocaine (self-report)	1.40 (1.6)	2.18 (1.7)	0.57 (1.0)	0.30 (.71)	0.80 (1.3)	24.695*
Cannabis (self-report)	1.26 (1.7)	3.00 (1.73)	2.07 (1.8)	1.59 (1.7)	1.80 (1.8)	14.799
Benzodiazepines (self-report)	1.86 (2.0)	3.09 (1.6)	2.64 (1.9)	1.80 (1.9)	2.13 (1.9)	10.574
Alcohol (self-report)	2.9 (1.4)	3.7 (0.9)	2.35 (1.7)	2.02 (1.7)	2.47 (1.7)	23.542*
			Change 2003-04			
Opiates (urine sample)						27.3***
Cocaine						11.7**
Benzodiazepines						11.79
Cannabis						11.01
Summation OP-CC-BZD						14.7
Opiates (self-report)						6.30
Cocaine						9.64*
Cannabis						3.49
Benzodiazepines						2.46
Alcohol						27.0**

* p<.05; ** p<.01; *** p<.001. Note: A specific result for the boxes of the change from year 2003 to 2004 is not included because each variable is a 4 x 4 table.

In general, a greater consumption was observed in those who continued without taking antiretroviral treatment, abstinence was observed in the case of those taking their medication adequately for the whole year, and particularly relapses in opiate and cocaine consumption and an increase in the frequency of alcohol intake were observed in dropouts. Nevertheless, those who started the antiretroviral treatment reduced their alcohol intake and gave up the use of opiates and cocaine. These results were not only shown in the consumption reports but also in the analytical samples.

An additional analysis dealt with the indicator of multi-consumption (Tables 2, 3, 4). The indicator of monthly compliance provided most information. Therefore, at Round 1, there was a difference between the participants who adequately continued and

Table 3. Adherence (Week) by drug use (urine sample, self-report).

Adherence to HAART	WEEK				Total	
	Abandon treatment	Continue treatment	Start treatment	Remain adherent		
N	15	16	13	39	83	χ^2
Year 2003						
Opiate (urine sample)	33.3%	50.0%	30.8%	2.6%	21.7%	17.77***
Cocaine (urine sample))	33.3%	62.5%	46.2%	15.4%	32.5%	12.87**
Cannabis (urine sample)	33.3%	75.0%	61.5%	43.6%	50.6%	6.98
Benzodiazepines (urine sample)	46.7%	75.0%	69.2%	46.2%	55.4%	5.30
Summation for OP-CC-BZD	1.13 (1.1)	1.87 (1.1)	1.46 (1.0)	.64 (0.7)	1.09 (1.05)	19.89*
Opiates (self-report)	0.86 (1.5)	1.62 (1.8)	.53 (1.1)	0.17 (.0.6)	0.63 (1.3)	22.72*
Cocaine (self-report)	0.66 (1.2)	1.62 (1.5)	1.23 (1.6)	0.43 (0.8)	0.83 (1.2)	16.06
Cannabis (self-report)	1.46 (1.8)	3.0 (1.5)	2.76 (1.6)	1.89 (1.9)	2.16 (1.8)	23.05
Benzodiazepines (self-report)	2.73 (1.2)	3.37 (1.0)	2.15 (1.6)	1.66 (1.6)	2.26 (1.6)	12.19*
Alcohol (self-report)	1.06 (1.2)	2.37 (1.5)	2.07 (1.5)	1.28 (1.6)	1.57 (1.5)	15.62
Year 2004						
Opiates (urine sample)	26.7%	25.0%	.0%	7.7%	13.35	7.303
Cocaine (urine sample))	18.1%	19.3%	15.4%	47.7%	33.7%	19.61***
Cannabis (urine sample)	53.3%	87.5%	61.5%	51.3%	60.2%	6.579
BZD (urine sample)	46.7%	87.5%	53.6%	48.7%	56.6%	7.849*
Summation for OP-CC-BZD	1.20 (1.1)	1.87 (0.8)	.69 (0.6)	.74 (.08)	1.03 (.96)	21.49*
Opiates (self-report)	.60 (1.2)	.56 (1.2)	.00 (0)	.07 (.35)	.25 (0.8)	20.504
Cocaine (self-report)	1.40 (1.6)	2.12 (1.5)	.15 (0.3)	.30 (.73)	.83 (1.3)	30.87**
Cannabis (self-report)	1.33 (1.6)	2.93 (1.6)	1.69 (1.7)	1.57 (1.8)	1.81 (1.7)	13.347
Benzodiazepines (self-report)	1.86 (2.1)	3.37 (1.4)	1.92 (2.01)	1.84 (1.9)	2.15 (1.9)	12.954
Alcohol (self-report)	2.93 (1.4)	3.81 (0.7)	2.07 (1.6)	1.92 (1.99	2.49 (1.7)	31.44**
Change 2003-04						
Opiates (urine sample)						27.7***
Cocaine						31.9***
Benzodiazepines						13.2
Cannabis)						10.3
Summation OP-CC-BZD						15.7
Opiates (self-report)						6.3
Cocaine						7.4
Cannabis						5.7
Benzodiazepines						3.1
Alcohol						31.3**

* $p < 0.5$; ** $p < .01$; *** $p < .001$
Note: A specific result for the boxes of the change from year 2003 to 2004 is not included because each variable is a 4x4 table.

those who were compliers at that time. However, at Round 2 this difference was statistically significant between those who continued adequately and those who did not. The categorical analysis of this variable showed also that the participants with a positive compliance change were associated with a reduced consumption.

As shown, compliance was significantly related to drug abuse for the three types of compliance considered. However, not all the drugs were equally valid to predict compliance values. In the case of compliance since the day before, the best predictive factors, by order of importance, were the change in the opiate analysis ($\tau = .140$) and

Table 4. Adherence (Month) by drug use (urine sample, self-report).

Adherence to HAART	Abandon treatment	Continue treatment	Start treatment	Remain adherent	Total	χ^2
			MONTH			
N	10	30	14	29	83	
Year 2003						
Opiates (urine sample)	30.0%	40.0%	14.3%	3.4%	21.7%	12.46**
Cocaine (urine sample))	20.0%	53.3%	28.6%	17.2%	32.5%	9.81*
Cannabis (urine sample)	30.0%	636.%	50.0%	44.8%	50.6%	4.03
BZD (urine sample)	30.0%	70.0%	71.4%	41.4%	55.4%	8.96*
Summation for OP-CC-BZD	.80 (1.3)	1.63 (1.1)	1.14 (0.8)	.92 (0.7)	1.09 (1.0)	21.97*
Opiates (self-report)	.90 (1.5)	1.1 (1.6)	0.5 (1)	0.13 (0.7)	0.63 (1.3)	20.78
Cocaine (self-report)	0.60 (1.3)	1.23 (1.4)	0.85 (1.4)	.48 (0.9)	0.83 (1.2)	15.51
Cannabis (self-report)	1.0 (1.6)	2.63 (1.7)	2.78 (1.5)	1.79 (2.0)	2.16 (1.8)	21.87*
Benzodiazepines (self-report)	2.50 (1.4)	3.16 (1.1)	2.14 (1.5)	1.31 (1.6)	2.26 (1.6)	31.28**
Alcohol (self-report)	.70 (1.1)	2.13 (1.52)	1.50 (1.6)	1.34 (1.65)	1.57 (1.5)	14.62
Year 2004						
Opiates (urine sample)	30.0%	16.7%	0.0%	10.3%	13.3%	5.096
Cocaine (urine sample))	40.0%	56.7%	7.1%	20.7%	33.7%	13.86**
Cannabis (urine sample)	50.0%	73.3%	57.1%	51.7%	60.2%	3.519
BZD (urine sample)	40.0%	73.3%	50.0%	48.3%	56.6%	5.608
Summation for OP-CC-BZD	1.10 (1.2)	1.46 (0.9)	.57 (0.5)	.79 (0.9)	1.03 (0.9)	19.60*
Opiates (self-report)	0.90 (1.4)	0.30 (0.9)	0.0 (0)	.10 (0.4)	.25 (0.8)	21.306*
Cocaine (self-report)	1.30 (1.7)	1.50 (1.5)	0.0 (0)	.37 (0.8)	.83 (1.3)	24.656*
Cannabis (self-report)	1.10 (1.7)	2.43 (1.7)	1.57 (1.6)	1.55 (1.8)	1.81 (1.7)	14.497
Benzodiazepines (self-report)	1.60 (2.0)	2.76 (1.8)	2.07 (1.9)	1.7 (1.9)	2.15 (1.9)	12.094
Alcohol (self-report)	3.10 (1.5)	3.46 (1.0)	1.7 (1.8)	1.65 (1.7)	2.49 (1.7)	27.13**
Change 2003-04						
Opiates (urine sample)						21.6**
Cocaine						20.5*
Benzodiazepines						16.6
Cannabis						6.0
Summation OP-CC-BZD						19.2*
Opiates (self-report)						8.5*
Cocaine						5.2
Cannabis						1.1
Benzodiazepines						9.2*
Alcohol						50.1***

*p<.05; **p<.01; ***p<.001. Note: A specific result for the boxes of the change from 2003 to 2004 in not included because each variable is a 4x4 table.

self-reported alcohol intake ($\tau = .134$), multi-consumption ($\tau = .124$) and use of opiates at Round 1 ($\tau = .112$), alcohol intake ($\tau = .100$) and cocaine use at Round 2 ($\tau = .109$), and change in the use of cocaine from Round 1 to 2 ($\tau = .109$). The remaining significant predictors (Table 2) showed tau index values below 0.1.

With regard to compliance for one week, the best predictors were the changes in alcohol intake ($\tau = .142$) and use of opiates ($\tau = .134$) and cocaine ($\tau = .132$), the consumption of alcohol ($\tau = .132$) and cocaine ($\tau = .132$) at Round 2 and the consumption of opiates ($\tau = .101$), multi-consumption ($\tau = .103$) and self-reported alcohol intake ($\tau = .105$) at Round 1. The remaining significant predictors (Table 3) showed tau index values below 0.1.

In the case of compliance for one month, alcohol was the most relevant factor, as the best three predictors were the change in alcohol intake from Round 1 to 2 (τ =.216), and self-reported alcohol intake at Round 1 (τ = .159) and at Round 2 (τ = .133). Alcohol intake was an indicator of multi-consumption at Round 1 (τ = .108), of cocaine analysis (τ = .109) and of changes in the use of opiates (τ = .106). The rest of the predictors which showed significant χ^2 values showed tau values below 0.1.

DISCUSSION

Although some improvements are required in the methadone program investigation (Fischer, Rehm, Kim, & Kirst, 2005; Pelet, Doll, Huissoud, *et al.*, 2005), there is some agreement which has led to a marked improvement for opiate dependent drug users. It is generally accepted that these programs have led to a general quality of life improvement (Fernández, González, Sáiz, Gutiérrez, & Bobes, 1999; Scherbaum, Kluwig, Specka, *et al.*, 2005), although it is not uncommon to come across participants who still use and abuse drugs (Martini *et al.*, 2004). This study clearly states that drug use within methadone maintenance programs is no doubt associated with other health behavioral patterns, such as following the antiretroviral treatment schedule. These data are not surprising, as we face two problems which may require chronic or long-term treatments. This is why we understand that a longitudinal study, such as that reported here, will provide additional information which can be used for other cross-sectional studies.

First of all, we have seen that, depending on the substances, some participants still continue with drug abuse (10% in the case of heroin, 21% in the case of cocaine, and up to 41% in the case of benzodiazepines) in addition to a lower percentage of participants with relapsing abuse. Something similar occurs with antiretroviral compliance: from 52% to 35%, depending on the time period considered, adequately maintain the treatment, whereas from 13% to 35% decide not to continue the treatment. There is a percentage from 12% to 18% of participants who modify their treatment compliance, because they either started it or they have discontinued it. Pooling these findings shows that all the categories appear to be related to each other: those who follow the treatment are more likely to be abstinent to drugs such as opiates, cocaine or benzodiazepines, or consume alcohol occasionally, whereas those taking these drugs are unlikely to have started any treatment. In the same way, those who relapsing consumption are more likely to discontinue the treatment and the start of the treatment appears to be associated with drug withdrawal. It also appears that not all the drugs have the same importance in this relationship, as cannabis is hardly relevant, as opposed to other studies (Braithwaite, Stephens, Conerly, Arriola, & Robillard, 2004), whereas cocaine has a clear importance to the changes of both behaviors. Opiates, on the one hand, appear to be associated with the longer evolution indicators, interfering with monthly compliance or with not taking the medication throughout the year. The increase or decrease in alcohol intake is also associated with compliance changes, which would again show the importance of this drug, particularly considering long temporal patterns, as in our study for one-month compliance (Stein *et al.*, 2002). Another study also demonstrated the importance of

different drugs for compliance, attributing different explanations to heroin and cocaine on the one hand, and on the other to benzodiazepines and alcohol (Martini *et al.*, 2004). Although this finding appears to be confirmed in this study, multi-consumption emerges with greater relevance than the use of one drug or the other alone (Ladero, Orejudo, Carrobles, & Malo, 2005).

An additional analysis is required. We have seen that the use of drugs and compliance are related, but we cannot establish a causal relationship between one event and the other. Nevertheless, there are some additional data that can support the precursory role of drug consumption. On the one hand, the nature of the behavior of consumption itself and of abstinence are associated with significant lifestyle changes (Vagner & Ryan, 2004), and in the case of the former, with a high interference with daily activities (Clarke, Delamere, McCullogh, *et al.*, 2003) so it is not surprising that the relapsing drug abuse is linked to treatment discontinuations. On the other hand, it must be noted that it is very likely that personal decisions of change start with drug abuse and then spread to other life areas, in both cases the center of attention to drug addicts being a reference point and support to initiate and maintain both behaviors as a general lifestyle change, which is evidenced by the relationship between the support perceived in the IADAC, family and compliance (Ladero, Orejudo, & Carrobles, 2005; Martínez, 2004).

It can be therefore concluded that participants who are drug users are more likely to discontinue HAART. Some relevant issues can be thus considered for the practice of professionals directly involved with HIV-AIDS patients on drug addiction withdrawal programs. We therefore wonder whether it would be more advisable to delay access to HAART for those participants who are active consumers, because the fact that the participants are very likely to discontinue the treatment would have adverse consequences not only for their health but also for the whole community, as this would involve significant costs for the health system.

Alternatively, it is essential to continue working with active drug users so that abstinence can be reached and they subsequently can access HAART. Many papers have been published to date that show that a minimum intervention achieves a significant increase in compliance with antiretroviral treatment for this community (Moatti, Carrieri, Spire, *et al.*, 2000; Malow, McPherson, Klimas, *et al.*, 1998). We must also stress the proven efficacy of the psycho-social intervention carried out by the IADAC for better achieving a successful methadone treatment (Fernández *et al.*, 1999; Scherbaum *et al.*, 2005).

All of the above requires close coordination between the different medical levels currently present in Spain for this community: hospital, IADAC, PMM, outpatient clinics. The IADAC can work on withdrawal and abstinence before referring a patient to a clinic. After this, the educational work can continue, monitoring compliance, and paying special attention to those participants who have more difficulties for compliance (homelessness, lack of social support, psychiatric disorders, taking other abuse drugs...), where other measures could be applied, such as drug administration directly from the center (directly observed therapy) and promote the training of peer groups, accessible from the center, with the multiple possibilities that open up and can increase the success of antiretroviral treatment (Broadhead, Heckathorn, Altice, *et al.*, 2002). These interventions

would be complemented by those designed by the clinics where the enhanced compliance can be observed from the intervention of the pharmaceutical service (drug accountability) and a minimum psycho-social intervention (Knobel, Codina, Miró, *et al.*, 2000).

REFERENCES

Avants SK, Margolin A, Warburton LA, Hawkins KA, & Shi J (2001). Predictors of nonadherence to HIV-related medication regimens during methadone stabilization. *American Journal of Addictions, 10*, 69-78.

Arnsten JH, Demas PA, Farzadegan H, Grant RW, Gourevitch MN, Chang CJ, Buono D, Eckholdt H, Howard AA, & Schoenbaum EE (2001). Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: Comparison of self-report and electronic monitoring. *Clinical infectious diseases, 33,* 1417-1423

Ballester R, (2003). Eficacia terapéutica de un programa de intervención grupal cognitivo-comportamental para mejorar la adhesión al tratamiento y el estado emocional de pacientes con Infección por VIH/SIDA. *Psicothema, 15*, 517-523.

Bermúdez MP & Teva I (2004). Situación actual del SIDA en España: análisis de las diferencias entre comunidades autónomas. *International Journal of Clinical and Health Psychology, 4*, 553-570.

Bouhnik AD, Preau M, Vincent E, Carrieri MP, Gallais H, Lepeu G, Gastaut JA, Moatti JP, & Spire B (2005). Depression and clinical progression in HIV-infected drug users treated with highly active antiretroviral therapy. *Antiviral Therapy, 10*, 53-61.

Bouhnik AD, Carrieri MP, Rey D, Spire B, Gastaut JA, Gallais H, & Obadia Y (2004). Drug injection cessation among HIV-infected injecting drug users. *Addictive Behaviors, 29*, 1189-1197.

Braithwaite R, Stephens T, Conerly RC, Arriola KJ, & Robillard A (2004). The relationship among marijuana use, prior incarceration, and inmates' self-reported HIV/AIDS risk behaviors. *Addictive Behaviors, 29*, 995-999.

Broadhead, RS, Heckathorn, DD, Altice, FL, Van Hulst, Y, Carbone, M, Friedland, GH, O'Connor, PG & Selwyn, PA (2002). Increasing drug users' adherence to HIV treatment: results of a peer-driven intervention feasibility study. Social Science and Medicine, 55, 235-246.

Clarke S, Delamere S, McCullogh L, Hopkins S, Bergin C, & Mulcahy F (2003). Assesing limiting factors to the aceptance of antirretroviral therapy in a large cohort of injecting drug users. *HIV Medicine, 4,* 33-37.

Chesney M (2003). Adherence to HAART regimens. *AIDS Patient Care & STDS, 17,* 169-177.

Fernández JJ, González MP, Sáiz PA, Gutiérrez E & Bobes J (1999). Calidad de vida y severidad de la adicción en heroinómanos en tratamiento prolongado con metadona. *Adicciones, 11,* 43-52.

Fischer B, Rehm J, Kim G, & Kirst M (2005). Eyes Wide Shut? A Conceptual and Empirical Critique of Methadone Maintenance Treatment. *European Addiction Research, 11*, 1-9

Gebo KA, Keruly J, & Moore RD (2003). Association of social stress, illicit drug use and health beliefs with nonadherence to antirretroviral therapy. *Journal of General Internal Medicine, 18*, 104-111.

Gordillo V, Del Amo J, Soriano V, & González-Lahoz J (1999). Sociodemografic and psichological variables influencing adherence to antiretroviral therapy. *AIDS, 13*, 1763-1769.

Gossop M, Marsden J, Stewart D, & Treacy S (2002). Change and stability of change after treatment of drug misuse. 2-year outcomes from National Treatment Outcome Research Study (UK). *Addictive Behaviors, 27*, 155-166.

Haubrich R, Little S, Currier J, Forthal D, Kemper C, Beall G, Johnson D, Dubé M, Hwang J, & McCutchan J (1999).The value of patient-reported adherence to antiretroviral therapy in predicting virologic and immunologic response. *AIDS, 13*, 1099-1107.

Haug NA, Sorensen JL, Lollo ND, Gruber VA, Delucchi KL, & Hall SM (2005). Gender differences among HIV-positive methadone maintenance patients enrolled in a medication adherence trial. *AIDS Care, 17*, 1022-1029.

Hill Z, Kendall C, & Fernández M (2003). Patterns of Adherence to Antirretrovirals: Why Adherence has no simple. *AIDS Patient Care & STDs, 17*, 519-525.

Hinkin CH, Hardy DJ, Mason KI, Castellon SA, Durvasula RS, Lam MN, & Stefaniak M (2004). Medication adherence in HIV-infected adults: effect of patient age, cognitivestatus, and substance abuse. *AIDS, 1, 18 Suppl 1*:S19-S25

Jensen-Fangel S (2004). The effectiveness of highly active antirretroviral therapy in HIV-infected patients. *Danish Medical Bulletin, 51*, 371-392.

Kerr T, Marshall A, Walsh J, Palepu A, Tyndall M, Montaner J, Hogg R, & Wood E (2005). Determinants of HAART discontinuation among injection drug users. *AIDS Care, 17*, 539-549.

Knobel H, Codina C, Miró JM, Carmona A, García B, Antela A, Gómez Domínguez MR, Arrizabalaga J, Iruin A, Laguna F, Jiménez I, Rubio R, Lluch A, & Viciana R (2000). Recomendaciones GESIDA/SEFH/PNS para mejorar la adherencia al tratamiento antirretroviral. *Enfermedades Infecciosas y Microbiología Clínica, 18*, 27-39.

Ladero L, Orejudo S, & Carrobles JA (2005). Variables psicosociales en la adherencia al tratamiento antirretroviral en pacientes adscritos a un programa de mantenimiento con metadona. *Psicothema, 15*, 573-579.

Ladero L, Orejudo S, Carrobles JA, & Malo C (2005). Consumo de drogas y adherencia al tratamiento antirretroviral de pacientes en programa de mantenimiento con metadona. *Adicciones, 17*, 203-214.

Malow R, McPherson S, Klimas N, Antoni M, Schneiderman N, Penedo F, Ziskind D, Page B, & McMahon R (1998). Adherence to Complex Combination Antiretroviral Therapies by HIV-Positive Drug Abusers. *Psychiatric Services, 49*, 1021-1022.

Martínez González JM (2004). Creencias y ajuste psicológico de la persona que acompaña al drogodependiente y creencias de éste durante el tratamiento. *International Journal of Clinical and Health Psychology, 5*, 43-66.

Martini M, Recchia E, Nasta P, Castonatto D, Chiaffarino F, Parazzini F, & Agnoletto V (2004). Illicit drug use: can it predict adherence to antirretroviral therapy? *European Journal of Epidemiology, 19*, 587-587.

Moatti JP, Carrieri M, Spire B, Gastaut J, Cassuto J, & Moreau J (2000). Adherence to HAART in French HIV-infected injecting drug users: The contribution of buprenorphine drug maintenance treatment. The Manif 2000 study group. *AIDS, 14*, 151-155.

Mocroft A, Johnson M, Lazzarin A, Clumeck N, Goebel FD, Viard JP, Gattell J, Blaxhult A, & Lundgren JD (1999). A comparison of exposure groups in the EuroSIDA study: Starting highly active

antiretroviral therapy (HAART), response to HAART, and survival. *Journal of Acquired Immune Deficiency Syndrome, 1*, 369-378.

Mohammed H, Kieltyka L, Richardson-Alston G, Magnus M, Fawal H, Vermund SH, Rice J, & Kissinger P (2004). Adherence to HAART among HIV-infected persons in rural Louisiana. *AIDS Patient Care STDS, 18*, 289-96.

Muga R, Egea JM, Sanvisens A, Arnal J, Tural C, Tor J, & Rey Joly C (2004). Impact of injecting drug use on the interruption of antirretroviral therapies. *Journal of Epidemiology & Community Health, 58*, 286-287.

Murphy DA, Marelich WD, Hoffman D, & Steers WN (2004). Predictors of antiretroviral adherence. *AIDS Care, 16*, 471-84.

Palepu A, Horton NJ, Tibbetts N, Meli S, & Samet JH (2004). Uptake and adherence to highly active antiretroviral therapy among HIV-infected people with alcohol and other substance use problems: the impact of substance abuse treatment. *Addiction, 99,* 361-368.

Pardo A & Ruiz MA (2005). *Análisis de datos con SPSS 13 Base*. Madrid, McGraw Hill.

Parsons JT, Rosof E, Punzalan JC, & Di Maria L (2005). Integration of motivational interviewing and cognitive behavioral therapy to improve HIV medication adherence and reduce substance use among HIV-positive men and women: Results of a pilot project. *AIDS Patient Care STDS, 19*, 31-9.

Pelet A, Doll S, Huissoud T, Resplendino J, Besson J, & Favrat B (2005). Methadone Maintenance Treatment in the Swiss Canton of Vaud: Demographic and Clinical Data on 1,782 Ambulatory Patients. *European Addiction Research, 11*, 99-106

Powell-Cope GM, White J, Henkelman EJ, Turner BJ (2003). Qualitative and quantitative assessments of HAART adherence of substance-abusing women. *AIDS Care, 15*, 239-49.

Reynolds NR, Testa MA, Marc LG, Chesney MA, Neidig JL, Smith SR, Vella S, & Robbins GK (2003). Factors influencing medication adherence beliefs and self-efficacy in persons naïve to antiretroviral therapy: A multicenter, cross-sectional study. *Journal of Acquired Immune Deficiency Syndromes, 33*, 185-193.

Riera M, De La Fuente L, Castanyer B, Puigventós F, Villalonga C, Ribas MA, Pareja A, Leyes M, & Salas J (2002). Adherencia a los fármacos antirretrovirales medida por la concentración de fármacos y el recuento de comprimidos. Variables relacionadas con una mala adherencia. *Medicina Clínica, 119*, 286-92.

Roberts K & Mann T (2003). Adherence to antirretroviral medications in HIV/AIDS care: An narrative exploration of one women's foray into intentional nonadherence. *Health Care for Women International, 24*, 552-564.

Scherbaum N, Kluwig J, Specka M, Krause D, Merget B, Finkbeiner T, & Gastpar M (2005). Group Psychotherapy for Opiate Addicts in Methadone Maintenance Treatment -A Controlled Trial 2005. *European Addiction Research, 11*, 163-171

Sharpe TT, Lee LM, Nakashima AK, Elam-Evans LD, & Fleming PL (2004). Crack cocaine use and adherence to antiretroviral treatment among HIV-infected black women. *Journal of Community Health, 29*, 117-27.

Smith SR, Rublein JC, Marcus C, Brock TP, & Chesney MA (2003). A medication self-management program to improve adherente to HIV therapy regimens. *Patient Education & Counseling, 50*, 187-199.

Spire B, Duran S, Souville M, Leport C, Raffi F, & Moatti JP (2002). Adherence to highly active

antiretroviral therapies (HAART) in HIV-infected patients: Fron a predictive to a dynamic approach. *Social Science & Medicine, 54*, 1481-1496.

Stein MD, Rich JD, Maksad J, Chen MH, Hu P, Sobota M, & Clarke J (2000). Adherence to antiretroviral therapy among HIV-infected methadone patients: effect of ongoing illicit drug use. *The American Journal of Drug and Alcohol Abuse, 26*, 195-205.

Stein MD, Charuvastra A, Anderson B, Sobota M, & Friedman PD (2002). Alcohol and HIV risk taking among intravenous drug users. *Addictive Behaviors, 27*, 727-736.

van Asten L, Zangerle R, Hernandez Aguado I, Boufassa F, Broers B, Brettle RP, Roy J, McMenamin J, Coutinho RA, & Prins M (2005). Do HIV dise ase progression and HAART response vary among injecting drug users in Europe? *European Journal of Epidemiology, 20*, 795-804.

Wagner GJ & Ryan GW (2004). Relationship between routinization of daily behaviors and medication adherence in HIV-positive durg users. *AIDS Patient Care STDS, 18*, 385-393.

Witteveen E & Van Ameijden E (2002). Drug users and HIV-Combination therapy (HAART): Factors which impede or facilitate adherence. *Substance Use & Misuse, 37*, 1905-1925.

Wood E, Montaner JSG, Braitstein P, Yip B, Schecter MT, O'Shaughnessy MVO, & Hogg, RS (2004). Elevated rates of antirretroviral treatment discontinuation among HIV-infected injection drug users: implications for drug policy and public health. *International Journal of Drug Policy, 15*, 133-138.