

Compliance with antiretroviral treatment in HIV/AIDS patients on a methadone maintenance program

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Título: La adhesión al tratamiento antirretroviral en pacientes VIH+ en programa de mantenimiento con metadona.

Resumen: Los avances recientes observados en los "Tratamientos Antirretrovirales de Gran Actividad" (TARGA), destinados a controlar e impedir el avance del VIH/SIDA, han supuesto una mejora importante en la calidad y expectativas de vida de muchos pacientes con dicha enfermedad. A pesar de ello, persisten algunas dificultades para conseguir el control de la enfermedad, tales como las limitaciones de acceso a los tratamientos en algunos países, las inherentes al consumo de cualquier fármaco (problemas de absorción, toxicidad...) y el abandono del tratamiento por parte de los pacientes. En este trabajo se lleva a cabo una revisión sobre la adhesión a la terapia antirretroviral en población drogodependiente. Se realiza un somero análisis de los cambios y mejoras experimentados en el mundo occidental en relación con el VIH/SIDA y en los servicios de atención especializada a las adicciones y se analizan las relaciones existentes entre la adhesión a la TARGA y algunas variables psicosociales y clínicas: ansiedad, depresión, estrés, apoyo social, autoeficacia, autoesfuerzo y consumo de drogas. Finalmente, se extraen determinadas conclusiones y se sugieren algunas líneas de intervención y de investigación futuras.

Palabras clave: Adhesión TARGA; programa de mantenimiento con metadona; consumo de drogas; variables psicosociales

Abstract: Recent advances in "Highly Active Antiretroviral Therapies" (HAART), aimed at controlling and preventing the spreading of HIV/AIDS, have improved the quality of life and life expectancies of many patients with this fatal disease. Nevertheless, a significant number of difficulties persist, such as the existence of individuals from disadvantaged groups, that traditionally have had difficulty accessing high-quality health care in some countries, who have not benefited from these treatments. Adverse drug reactions and non compliance with treatment regimens increase the problems for the control of the disease. This work reviews studies on compliance with antiretroviral treatments regimens in injection drug users. We briefly went over the changes and improvements in HIV/AIDS and specialized drug addiction management services in the developed world and analyzed the relationship between HAART compliance and some psychosocial and clinical variables: anxiety, depression, stress, social support, self-efficacy, self-effort, and drug use. Finally, our review study suggests broad future intervention and research lines.

Key words: Compliance HAART; methadone maintenance program; drug use; psychosocial variables.

Introduction

Human immunodeficiency virus (HIV) infection is the most aggressive pandemic of recent decades. After the advent of antiretroviral treatments in the 90s, many advances have been made in the control of this disease, though HIV-infected patients from poor countries cannot always have access to drug therapies (OMS, 2006). In developed countries, HIV/AIDS infection is not more terminal, and has become a chronic disease, so concerns focus the search for an effective vaccine, preventing infection, reducing drug costs, making the treatments available to all infected patients, and achieving the greatest compliance (Nischal, Khopkar and Saple, 2005).

Despite multiple efforts by pharmaceutical companies to achieve a reduction in the number of drugs and reduce their toxicity, the main threat faced by healthcare professionals is non-compliance with treatment regimens.

It is estimated that an average of 40% of patients do not comply adequately with the treatment advice from their physicians, which means two of every five patients (DiMatteo, Linn, Chang and Cope, 1985). Literature data on antiretroviral compliance (HAART) estimate a non-compliance rate ranging from 15 to 37% (Ioannidis et al., 1997). This is even more relevant because some authors consider that taking

below 95% of the drug prescribed already involves a risk of increased viral load and reduced T4 cell count, with the subsequent appearance of resistant strains. This has raised a growing interest in this pandemic among healthcare professionals that monitor and design customized treatments. The most recent studies are maybe therefore obtaining higher compliance rates, averaging from 43% to 78% (Osterberg and Blaschke, 2005). The drug-addict population shows compliance rates from 62% to 58% when considering the criteria of drug administration that day and the week before (Ladero, Orejudo and Carrobbles, 2005a). These compliance levels are within the ranges found for other populations infected or for any other chronic disease, and are highly positive in the case of patients included in the methadone treatment program for an average of six years

In any case, a comparison among the different studies is difficult, since the samples, method, procedure, etc., are not always consistent. In addition, the high variability and complexity of compliance patterns hinder the assessment of factors influencing it, so it is also difficult to implement intervention programs which help improve it. Some taxonomies classify in four major groups the factors influencing compliance: a) factors related to the treatment regimen: type, complexity, behavioral demand, length, cost-benefit, efficacy, side effects, social environment, b) psycho-social issues of the patient: cognitive, emotional, social, social support, c) relative to the disease involved: acute or chronic, and d) interaction with healthcare professionals (Rodríguez-Marín, 1995).

Variables influencing treatment compliance have been

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tested in other diseases, such as schizophrenia, and the factors to be considered have been found to be the same as those for HAART compliance (Hudson et al., 2004) which helps guiding to some extent the interventions to be implemented with the different populations.

HIV/AIDS and treatment with methadone

In Spain, the maximum HIV transmission levels occurred between 1985 and 1988 and since then the new infection rate has decreased progressively. Since 2002 the reductions remain below 10% and the new diagnosis rate was 58 cases/million inhabitants in 2004; however, Spain is still one of the Western Europe countries with more people living with HIV. The population of injection drug users shows the highest prevalence of HIV/AIDS infection in our country (Centro Nacional de Epidemiología, 2007).

Methadone programs started to be implemented in Spain in the 90s, in part to try to minimize the results of substance injection in the health of drug abusers (HIV, hepatitis, tuberculosis...). There are other programs which also are intermediate solutions to total drug withdrawal: Damage Reduction Programs (DRP) and Syringe Exchange Programs (SEP). These have arisen for drug-addicts not using the healthcare network or choosing an active drug abuse (Alvarez, 1993).

Maintenance methadone programs have been recently made more flexible, to the extent of making access to treatment easier; patients are offered programs with various demand levels, monitoring the quality of treatments with sufficient doses, taking caring for their continuation in the program and, in some cases, the possibility of continuing in the program indefinitely is considered (Plan Nacional sobre Drogas, 2002).

Methadone alone has been shown to be not enough, though it is a valid instrument as an approach to reduce damages. It appears to be clearly demonstrated that programs with high doses, high demands and offering psychosocial resources yield the best outcomes (Scherbaum et al., 2005; Esteban, Gimeno, Barril and De la Cruz, 2004).

The addition of treatments with buprenorphine has meant another option for intravenous drug abusers suffering HIV+, since heroine consumption and the use of the intravenous route can be reduced, enhancing social stability and compliance with antiretroviral treatment, thus contributing to improve the quality of life of these patients (Basu, Smith-Rohrberg, Bruce and Altice, 2006).

Compliance with antiretroviral treatment in drug addicts

A previous condition to improve compliance is to know the factors related to it. Multiple studies relate it to sociodemographic variables, use of substances, symptoms of depression, quality of life, CD4 cell count, knowledge and beliefs

on the treatment, patient satisfaction with the services and easy relation with patients (Ammansari et al., 2002).

However, there are many difficulties in the study of compliance in drug-addicts, related to the methods (design) and type of study population (Ammansari et al., 2002). The drug addict population appears to have the lowest compliance with HAART maybe due to its characteristics: drug abuse, social problems, mental disorders, difficult access to resources, etc.; however, the study on compliance in this population can help achieving a greater access to antiretroviral treatments, and a better compliance with them.

Factors such as symptoms and drug-related side effects, psychological distress, low social or family support, the complexity of the dosing regimen, low self-efficacy and treatment inconveniences are related to non-compliance (Ammansari et al., 2002). In a recent study performed by Malta, Strathdee, Magnanini and Bastos (2008) that reviewed the studies published in different languages about compliance with HAART in drug-addict population, low compliance was associated with drug abuse, imprisonment and HIV comorbidity and psychiatric disorders, while, on the contrary, access to complete services, access to treatment for their drug dependence problem and psychosocial support were predictors of compliance.

In the studies performed in our country age (the younger the age, the lower the compliance), complexity of the regimen, history of injection drug use and greater anxiety have been found to be factors associated with non-compliance (Escobar et al., 2003).

Several authors have reported the significance of social variables such as educational level (Reynolds et al., 2004), age (Hinkin et al., 2004), employment (Carballo et al., 2004), not living alone, and imprisonment (Kerr et al., 2005) for HAART compliance in HIV/AIDS-infected patients. A relationship has been also found between psychological variables such as depression, anxiety and stress and compliance with antiretroviral treatment, evidencing that, when mental disorders are treated, in addition to drug addiction problems, compliance with HAART is increased (Pence, Miller, Gaynes and Eron, 2007).

Although there are multiple studies on the relationship between HAART compliance and a cross-sectional design, there are not so many studies with a longitudinal design. With this regard, compliance appears to decrease over time (Ladero, Orejudo and Carrobles, 2008). A multicenter, prospective study performed by the authors Howar et al. (2002) reported that compliance had decreased by 10% in six months. However, other authors assure that compliance does not decrease over time when some interventions are implemented. In fact, in a two-year follow-up Ostrop, Hallett and Gill (2000) reported that setting priorities and medical advice throughout the treatment caused that patient compliance did not decrease. For this, a customized treatment was performed, previously identifying patients with low compliance; physicians could help optimize compliance choosing adequately drugs based on patient's routine and

performing a follow-up with information, feedback and regular reminders of the dosing process.

Variables that can predict longitudinally compliance were also analyzed. Therefore, Carrieri et al. (2003) found that factors such as the lack of stable social relations, active injection drug use and severe depression are associated with treatment withdrawal in the drug-addict population. Although these patients were given counseling for maintaining compliance, there might be other factors not approached to explain this outcome, including prevention of drug abuse, provision of social supply or not considering the potential impact of difficulties when starting psychological support.

Of the variables explaining non-compliance with HAART in this population, drug abuse is one of the most significant hindrances (Battaglioli-DeNero, 2007; Hinkin et al., 2007). Although methadone can increase maintenance of patients treated for their drug abuse problem, the injection practice in active drug abuse appears to be one of the factors hindering compliance with HAART, while for patients on withdrawal the factor associated with non-compliance would be social instability (Bouhnik et al., 2002).

For drug-addicts, approaching social difficulties is very important to increase compliance.

Psychopathological variables in compliance with HAART

Psychopathological variables appear to be another potential group of predictive factors of compliance. However, studies on HIV/AIDS and mental disorders comorbidity have no large samples, are cross-sectional, have limitations in the control of tests, and the mental health and drug population is not well identified (Chadler, Himelhoch and Moore, 2006). Nevertheless, it appears, on the one hand, that the presence of a higher prevalence in HIV+ is confirmed to be higher in individuals with mental disorders than in the general population, though it is true that it is difficult that these patients complete the test to identify the infection and, on the other hand, that the use of drugs and mental disorders in HIV+ are associated with a low compliance. Therefore, a preventive intervention also appears to be required, including early detection of the virus and treatment in subjects with HIV/AIDS and mental disorders comorbidity (Weiser, Wolfe and Bangsberg, 2004). However, each disorder may have unique characteristics.

In fact, in schizophrenic patients the outcomes of the studies suggest a higher probability for low compliance when their educational level is low and are drug abusers, as they have greater barriers of access to services (stigma, more side effects experienced with the medicinal products, missing doses and lack of social support). However, other studies show that these patients are good compliers with the antiretroviral therapy, provided it is not a very complex regimen and they have support for the treatment (Leclerc et al., 2005).

Other clinical variables, such as anxiety, depression, drug abuse and alcohol dependence/abuse show that, the greater the presence of mood disorders (anxiety) and substance abuse, the lower the virological suppression (Pence et al., 2007). HIV+ infected population appears to have higher depression rates than the general population, that worsen with age and thus affect adversely compliance with HAART (Cook et al., 2004).

Some studies associate cognitive impairment (particularly performance functions and psychomotor fastness), substance abuse (except for alcohol intake), and age (the older the age, the greater the compliance), with antiretroviral treatment compliance (Hinkin et al., 2004). Significant relationships have been also found between compliance with HAART and higher levels of anxiety, depression and stress in drug-addict populations (Gordillo and de la Cruz, 2003; Reynolds et al., 2004).

In studies performed with samples of drug-addict population in our country, in addition to evidencing the significant relationship between compliance with HAART and higher levels of anxiety, depression and stress (Gordillo and de la Cruz, 2003), cross-sectional data analyses have demonstrated a clear relationship between psychological adjustment and compliance with antiretroviral therapy. However, taken longitudinally, anxiety, depression and stress are shown not to discriminate among the different patient groups prospectively (those continuing compliance, those not starting treatment, those discontinuing and those starting HAART during the study year). Although the compliance changes experienced by participants cannot be predicted, variations are found in association with compliance changes, improving in those starting therapy and worsening in those discontinuing it (Orejudo, Ladero, Carrobles and Malo, 2006). Therefore, given the complexity of compliance behaviors, it is necessary to distinguish at least between drug start, maintenance and discontinuation behaviors.

Patients with good compliance levels over time also show better emotional markers (Orejudo et al. 2006). This could be explained, in part, by the favorable expectations generated when coping successfully with the disease or by other variables that could also affect compliance and reduce stress, including social support or the patient's coping ability (Carrobles, Remor and Rodríguez-Alzamora, 2003).

On the contrary, patients who do not take their medicine over time show the worst adjustment levels: greater levels of anxiety, depression and stress (Orejudo et al. 2006). These results can be in part due to the personal failure for not taking the medicine or can be associated with other circumstances, such as drug abuse, present in this population, or the refusal to take the medicine for not believing in it, not tolerating side effects, previous unsuccessful attempts, that have reduced self-efficacy, another predictor of compliance (Pinheiro, de Carvalho-Leite, Drachler and Silveira, 2002). In any case, the worst emotional state of these patients, together with the lack of treatment, lead them to a double risk status, particularly considering that, as the disease progresses, psy-

chological factors such as depression become prognostic of a faster progression (Cook et al., 2004). Although it might be considered that emotional problems in HIV patients are the same as in any subject with a serious disease, some studies performed (Edo and Ballester, 2006) show that HIV patients experience significantly higher levels of anxiety and depression and lower levels of self-esteem than cancer patients.

Finally, some patients make changes over time, some start and other discontinue antiretroviral therapy. Those starting HAART during the year improve their psychological adjustment levels (anxiety, depression, and stress), and those discontinuing the treatment follow the same group approach trends as those not starting treatment, worsening the anxiety, depression and stress levels and with a situation opposite than the year before (Orejudo et al., 2006). The reasons why patients on a methadone maintenance program do not start antiretroviral therapy do not appear to be clear, but they are clear for those starting or discontinuing it, mainly in association with treatments of drug dependences and relapses (Muga et al., 2004).

It can be concluded that, though it is difficult to establish that some of the variables considered here help predict directly compliance changes, considered in high compliance levels, it appears that they may be relevant in maintaining established behaviors, either directly, either through treatment-modulating variables, such as self-efficacy, a relationship proven in other studies (Ladero, Orejudo and Carrobes, 2005b), lifestyle (Wagner and Ryan, 2004), social support (Carrobes et al., 2003), or drug abuse (Ladero et al., 2005a; Orejudo, Ladero, Carrobes, Malo and Almendros, 2009). In addition, when intervention programs are designed to enhance compliance in drug-addict populations, improving patient emotional status should be considered, particularly when some interventions have shown that compliance is enhanced when this issue is considered (Ballester, 2003).

Social support and self-efficacy in compliance with HAART

Social support plays a major role for the treatment of drug addiction, as improvement is seen in withdrawal and relapses, thus also with enhanced compliance when patients have a greater social reinforcement and better treatment support. Therefore, drug-addicts feeling that they are further supported by care providers in drug-addiction management centers, with lower barriers of access to resources and further emotionally supported by their relatives and/or friends have a higher probability for reaching withdrawal than those lacking this support (Skeie, Brekke, Lindbaek and Waal, 2007). In interventions performed with groups of relatives and friends of patients on methadone it is shown that an increased social support can reinforce withdrawal, so it can be expected that this in turn influences compliance with antiretroviral therapy (Kidorf et al., 2005).

Some studies show clearly the relationship between the

perception of social support and antiretroviral therapy compliance both in the general population (Waddell and Messeri, 2006) and the drug addict population on methadone maintenance program (Kidorf et al., 2005).

In HIV-infected drug users on methadone maintenance programs there is a clear relationship between social support felt both from the Drug-Addiction Management Center (CAID) and from relatives/friends, and compliance with antiretroviral therapy (Ladero, Orejudo and Carrobes, 2010). In this case, social support is a variable which enables to predict the start of antiretroviral therapy in these patients that also improve their perceived support over time. On the contrary, patients discontinuing antiretroviral therapy show a loss of support and obtain levels similar to untreated subjects.

The studies performed in drug-addicts on a closed regimen show as determinant factors to start antiretroviral therapy the trust in the treatment and the physician-patient relation, while for compliance reduction the related factors were side effects, social isolation, and complexity of the treatment regimen. The factors that could predict compliance were the characteristics of the physician and the degree of social isolation (Chen and Rosenheck, 2001). The role of physicians is essential to increase compliance in HIV+ drug-addict patients; for this, professionals must know the disease process, have a critical thinking and the skills to move adequately in the health system. Some authors recognize the importance of this behavior, assuring that to increase the access to treatment in drug-addict patients with mental disorders physicians should offer and train patients, giving them the opportunity to develop a plan that cancels low compliance and the complete support they need (Maisels, Steinberg and Tobias, 2001).

Various interventions show how achieving family support and removing the barriers to access to control medical therapies for HIV/AIDS can increase compliance with antiretroviral therapy (Shelton, Golin, Smith, Eng and Kaplan, 2006). Methods to increase compliance, such as Directly Observed Therapy (DOT), have been shown to be effective (Chadler et al., 2006). In HIV+ drug-addict population with physical and mental diseases it has been also shown that when the pharmacy staff collaborates in the DOT using electronic monitors as a compliance measurement, this is increased. The pharmacy staff usually associates interventions with social support, helping select antiretroviral therapy, monitoring it and identifying drug problems (Foisy and Akai, 2004); this once again evidences the relationship of social support with compliance. These outcomes would support the need for adding social support measures when designing interventions that attempt to make HAART available to marginal populations (Chen and Rosenheck, 2001).

In drug-addict patients, in addition to social support, other variables should be seemingly considered that could be mediating in the relationship with compliance. Among these, the role of drug abuse appears to be particularly relevant, since this use would interfere with compliance, also affecting

social support (Knowlton et al., 2006) and, as noted, there is an indirect relationship between drug use and compliance with HAART (Chen and Rosenheck, 2001). In the case of patients with a history of drug use, the start of antiretroviral treatments is usually simultaneous with the start of drug withdrawal programs, though discontinuations can subsequently occur in both programs (Muga et al., 2004). Many drug-addiction management centers, in addition to taking advantage of the benefit offered by the methadone program, include treatment for HIV/AIDS working on compliance with HAART and also for other diseases such as hepatitis C (Papelu, Horton, Tibbetts, Meli and Samet, 2004) and tuberculosis (Batki, Gruber, Bradley, Bradley and Delucchi, 2002).

Another variable tested in HAART compliance is self-efficacy. The results of studies investigating the relationship between self-efficacy and compliance with antiretroviral therapy support this relationship, though the authors do not always agree in the predictability of this variable (Kerr et al., 2005). Therefore, we found studies in HIV+ infected population, PDA with mental health problems, where the reasons claimed by the patients where HAARTs were recommended and not starting it were that they were not able to comply fully with the treatment regimen and their fear for side effects. Other reasons were the active drug abuse, religious beliefs, homelessness, concern for confidentiality, depression or feeling of wellbeing without HAART. Physicians not recommending HAARTs claimed the active drug abuse and the fact that there was no commitment with the physician, homelessness, higher depression levels and also perception that the patient was feeling well without antiretroviral therapy (Maisels et al., 2001). Other studies reported similar results both in patients without (Tuldrá et al., 1999) and with a history of drug abuse (Pinheiro et al., 2002; Reynolds et al., 2004).

It can be generally assured that compliance is higher in patients feeling they are more able to continue treatment, as shown in a recent study in drug-addict population (Ladero, Orejudo y Carrobes, 2008). Self-efficacy is also seen to progress in relation to compliance with HAART and contrary to the effort perceived, so patients who remain compliers or starting therapy increased their perceived self-efficacy levels (Ladero et al., 2008). This result shows a pattern contrary to the loss of self-efficacy experienced by patients discontinuing the drug, reaching levels similar to those previously untreated, in turn increasing the effort to continue with it.

No doubt one of the most feasible explanations for the low perception of self-efficacy and great effort perceived in patients not starting antiretroviral therapy or in those discontinuing drug abuse, as these uses occur in patients on methadone maintenance programs (Ladero et al., 2005a). In addition, other variables that could influence self-efficacy and through it compliance rates must be also highlighted, such as visits to the center, discontinuation of psychological therapy, increased anxiety, depression and stress levels and

perception of social support lost from the CAID (Ladero et al., 2005b).

The predictive role of self-efficacy in compliance has been also shown in other diseases with complex treatment regimens, including hypertension (García-Pavía et al., 2007) or diabetes. In other type of diseases, such as rheumatoid arthritis and polymyalgia, compliance is seen to decrease in the 6-month follow-up in all patient groups studied; also the groups show differences in compliance depending on the type of disease, acute or chronic, frequency of dosing, sex, coping skills, and health in general (De Kler et al., 2003). The studies evaluating the relationship between compliance in diabetes and self-efficacy report that patients receiving comprehensive information about self-administration of insulin in addition to a good preparation obtain a better self-efficacy level for the treatment and depression and anxiety levels decrease, while those receiving information alone show a lower self-efficacy level and, therefore, a lower compliance (Matteucci and Giampietro, 2003). In the psychological intervention programs in patients with cancer it is proven how this intervention can be improved when the self efficacy increases in themselves (Báñez, Blasco and Fernández, 2003).

Other variables related exactly to the treatment regimen, such as automation of approaches in medicine use could explain the persistence of adequate compliance levels. The use of reminding approaches to take the medicine appears to be a highly adaptive approach to continue the prescription of the treatment regimen when this involves a high behavior demand and complexity, as in the case of HAARTs. In this case it has been found that the participants not needing any external stimulus (notes in strategic places, pill boxes, warning alarms, help from others –relatives, physician, prison officer-, etc) to remember dosing show a higher probability for optimum compliance (Ladero et al., 2005b).

Drug use in compliance with haart

Drug use has been established to affect compliance (Battaglioli-DeNero, 2007; Hinkin et al., 2007). Ladero et al. (2005a) report the influence of drug use in compliance with antiretroviral therapy in patients on methadone maintenance programs. This relationship is virtually the same for all types of abuse drugs (opioids, cocaine, benzodiazepines, alcohol and cannabis), for both methods of consumption assessment considered (self-report and urine tests) and for most markers of compliance considered (of the day, the week and the month before, with highest and low demand criteria). With this regard, the importance of polyconsumption in compliance is to be noted. Therefore, low-demand markers of compliance of the day before, the week before and the month before include the marker comprising use of opioids, cocaine and benzodiazepines as its first predictor, which means that participants using these substances show a lower probability for being good compliers than those using two

and these in turn lower than those using a single drug (Ladero et al., 2005a).

Considering compliance longitudinally and analyzing the changes in it and in drug use, patients who continue on antiretroviral therapy are seen to remain abstinent, those starting no antiretroviral therapy are usually active users of heroine, cocaine, benzodiazepines and alcohol, those starting some cycle of HAART discontinue the use of opioids and cocaine, reducing also alcohol intake and, finally, those discontinuing treatment with HAART relapse in active use of heroine, cocaine, benzodiazepines and increase alcohol intake (Orejudo et al., in press). Relapsing use of heroine, cocaine, benzodiazepines and excessive alcohol intake enhance discontinuation of HAARTs, while the use of cannabis and moderate use of alcohol do not increase the possibility for discontinuing antiretroviral therapy. Similar outcomes were reported in other studies (Perretti-Watel, Spire, Lert and Obadia, 2006), describing that the use of drugs, such as tobacco or cannabis, was only associated with low compliance when their use was associated with the use of abuse drugs such as heroine and alcohol at high amounts.

Other cross-sectional studies report the relationship between use and disease progression. Therefore, Papelu et al. (2004) reported that, after six months, viral suppression was favorably associated with high doses of medicines and older age and adversely with the use of alcohol and abuse drugs in the previous month. Surprisingly, substance abuse was associated with the start of antiretroviral therapy, but not with viral load suppression. Furthermore, the more the symptoms of depression and the higher the drug and alcohol abuse by the patients, the worse the compliance levels reported in the assessment performed one month later.

Other cross-sectional studies investigating the changing nature of the use of substances and time association of this use with the effects of treatment with HAART, show how changes in the use of substances by abstinent were associated with an increased use of HAART, improved compliance and outcomes of HIV+ treatment, while those who continued using worsened in the use of HAART, compliance and treatment outcomes (Lucas, Gebo, Chaisson and Moore, 2002). A cross-sectional study performed by Pach, Cerbone and Gerstein (2003), evaluating the impact of drug use in compliance considering social barriers, reports that the difficult access to services by drug-addict population makes their life conditions not to not improve and that they do not benefit from antiretroviral therapies.

Some authors question the influence of drug use in HIV+ infection as, in some subset of patients in a follow-up of several days later, drug use was found not to influence compliance reduction, while in another group of patients it did; therefore, the effects of drug use contribute to non-compliance in some specific drugs and depending on the day when they are used (Rosen, Rigsby, Dieckhaus and Cramer, 2003).

These outcomes could be explained by the lifestyle changes occurring in patients in methadone programs that

help discontinuing toxic habits and getting healthy habits, including the start of antiretroviral therapy. It is clear that drug-addiction management programs provide an incomparable environment to work on compliance with antiretroviral therapy and jointly with other measures can largely benefit these patients.

Therefore, directly observed therapy in the drug-addict population can increase compliance, provides social support and can coordinate the different services –social services, drug-addiction management, psychiatric and other services – helping drug-addicts to implement necessary behavior changes (Smith-Rohrberg, Mezger, Walton, Bruce and Altice, 2006 Garcés y Durá, 1992). Furthermore, other measures, such as the use of reinforcement to improve compliance, have been tested. In interventions performed with systems of incentives and rewards, compliance can be enhanced in drug-addict patients on methadone programs (Haug, Sorensen, Gruber, Lollo and Roth, 2006). Some studies go further and reinforce compliance with money and even increase it in marginal and drug-addict population; however, compliance did not increase beyond the training period, and the issue related to the time and length of intervention requires further studies (Rigsby et al., 2000).

Therefore, some authors appeal to the need for developing designs and techniques that reproduce as accurately as possible the natural conditions of HIV+ infection and that represent the additional assessments of laboratory tests, clinical and epidemiological data which establish the actual impact of drug abuse in HIV+ infection (Khalsa and Royal, 2004). Factors such as drug abuse, and others considered in different studies, such as self-efficacy, social support perceived, negative emotional states, as well as other issues, including the difficulties characteristic of the regimen or pharmacological issues -toxicity, drug interactions, etc.- can help understand a behavior as complex as compliance with HAART.

Conclusions

As discussed above, access to antiretroviral therapy by HIV/AIDS patients does not currently involve a major problem in developed countries; however interventions to reach the goal of starting and maintaining HAART, particularly in drug-addict HIV/AIDS populations, do not appear to be as effective as desired, despite research and intervention advances.

The literature reviewed on intervention programs that can enhance compliance advocate directly observed therapy (DOT), as they are usually supplemented with social support from healthcare professionals. However, it would be interesting to continue investigating through cross-sectional studies other variables that could become predictors of maintenance of HAART, once control by other parties is removed and when the patient should become independent and responsible for his/her treatment. With this regard, it

must be noted that the pharmaceutical industry has made a significant effort designing growingly simpler treatments (one tablet/24 hours) that may enhance automation of administration behaviors in patients affected by HIV+ infection.

The use of psychoactive substances by HIV+ population must be highlighted; in fact, future research should be aimed at establishing both the type of substances used and the method and frequency of use that could affect more clearly compliance and, as suggested, the maintenance or discontinuation of HAART, since, as we have shown, not all uses appear to be equally problematic.

In the case of negative moods, their importance in compliance and development and progression of infection has been shown in this review study, and it would be important, in this research line, to establish the influence of negative life events of patients and their relationship with variables such as depression, anxiety, stress, self-efficacy or effort for the treatment. In the case of drug addict populations in our country, many have problems of unemployment, imprisonment, losses for partner or friends death, etc., which, together with their health problems, make them a high-risk population for experiencing these negative mood states, with a

greater possibility for relapses in active drug consumption and, therefore, many difficulties to keep an adequate compliance (Castellanos, 2007).

Given the above, it is logical to think of integral intervention programs approaching all issues related to addiction and the health problems resulting of it. The resources that Integral Drug-Addiction Management Centers should use would include working with peer groups, as it would be a source of social support that could change attitudes in health-related concerns and obviously compliance with HAART's.

And all considering the importance of the complexity of compliance, with the different changes that can occur in it and considering that not necessarily the same factors can influence its start, maintenance or discontinuation (Orejudo et al., 2006). Finally, it must be highlighted that the HIV/AIDS research and interventions generated in recent years have enabled us to move from a disease with an unfavorable prognosis to another that eventually becomes chronic, that we must face with its new characteristics, and in this case the problem of compliance becomes a star that investigators, healthcare professionals and pharmaceutical companies must continue approaching.

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