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ORIGINAL ARTICLE

Factors associated with adherence in HIV patients

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Abstract
Objective: To establish the relationship between the adherence to ARVT and the clinical situation and detect those factors which relate to the lack of adherence.
Method: Observational study on HIV patients who had attended the Pharmacy Service in Hospital de Navarra between February and May 2005. The SMAQ questionnaire and pharmacy dispensing records were used to assess adherence to treatment. Socio-demographic variables and other factors which could infl uence adherence were recorded. Statistical analysis was carried out using the SPSS programme, version 14.0.
Results: No concordance was noted between the 2 measurements of adherence, although there was an association between the viral load and compliance, irrespective of the method used. The questionnaire recorded a higher percentage of non-adhering female patients, substance users and psychiatric patients. Non-adhering patients indicated more frequently factors which made taking the medication difficult. The multivariate analysis showed that the lack of a suitable social-familial environment negatively influenced the adherence level, according to the SMAQ questionnaire, and that the high number of tablets per dose was related to the lack of adherence according to the pharmacy dispensing records.
Conclusions: Patients who adhere to ARVT have a lesser risk of virological failure. An unsuitable social-familial environment and the complexity of treatment are associated with a lack of adherence. The method of using dispensing records should be combined with a patient interview to define the factors which reduce adherence and to propose intervention strategies.

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PALABRAS CLAVE
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Factores relacionados con la adherencia en pacientes infectados por el virus de la inmunodeficiencia humana

Resumen
Objetivo: Establecer la relación entre adherencia al tratamiento antirretroviral (TARV) y situación clínica, y detectar los factores que se relacionan con la falta de adherencia.
Método: Estudio observacional en el que se incluyó a pacientes infectados por el virus de la inmunodeficiencia humana que acudieron al Servicio de Farmacia del Hospital de Navarra entre febrero y mayo de 2005. Para evaluar la adherencia al tratamiento, se utilizó el cuestionario SMAQ (Simplified Medication Adherence Questionnaire) y el registro de las dispensaciones. Se recogieron variables sociodemográficas y otros factores que podrían influir en el cumplimiento. El análisis estadístico se realizó mediante el programa SPSS versión 14.0.
Resultados: No se observó concordancia entre las 2 medidas de adherencia, aunque sí asociación entre carga viral y cumplimiento, independientemente del método utilizado. Se obtuvo un porcentaje mayor de pacientes no adherentes según el cuestionario, en mujeres, consumidores de sustancias y pacientes psiquiátricos. Los pacientes no adherentes señalaron con más frecuencia factores que dificultan la toma de la medicación. En el análisis multivariante, se observó que la carencia de un entorno sociofamiliar adecuado influye de forma negativa en la adherencia medida según el SMAQ y que el elevado número de comprimidos por toma se relaciona con la falta de adherencia según el método de registros de dispensación.
Conclusiones: Los pacientes adherentes al TARV tienen un riesgo menor de presentar fallo virológico. Un entorno sociofamiliar inadecuado y la complejidad del tratamiento se asocian con la falta de adherencia. El método de registros de dispensación se debe combinar con la entrevista al paciente para detectar factores que disminuyen la adherencia y proponer estrategias de intervención.

Introduction

Adherence to antiretroviral therapy (ARVT) is one of the key factors in the follow-up of patients infected with human immunodeficiency virus (HIV), since in many cases it can determine the treatment's success or failure.[1,2]

In the mid-1990s, when highly active antiretroviral therapy (HAART) appeared, doctors were able to control viral replication, thus slowing the infection's clinical progress and significantly increasing patients' survival and quality of life. However, obtaining these benefits requires a strict level of adherence to the prescribed treatment in order to avoid the rapid evolution of resistance which results in the infection progressing and the patient having more difficulty finding effective treatments at a later time. From the viewpoint of public health authorities, this would increase the risk of transmitting resistant strains among the population, and given the high cost of these treatments, it causes inefficient use of public resources.[3]

It is known that total adherence to HAART is difficult and that it is not achieved by a high percentage of patients, despite its importance. Determining what factors make HAART adherence more difficult is extremely interesting, as it enables us to propose intervention strategies.

Currently, there are several methods for evaluating adherence,[2,4] although the ideal one is not known. This results in the numerous studies being done on different methodologies in order to provide useful tools. The literature recommends combining at least 2 methods in order to compensate the drawbacks that each one may have separately, thus obtaining the closest possible estimate to the real data.[2]

The questionnaires are simple, inexpensive methods that can be adapted to different environments, and they are the only tool that informs us of the motives for poor adherence. Among those that have been validated for the Spanish population, we find the Simplified Medication Adherence Questionnaire (SMAQ).[5]

Adherence has become one of the most important aspects of HAART and it is of great interest to the scientific and social communities. This is demonstrated by the high number of studies published with the goal of contributing knowledge about and sharing experiences on this matter.

The objective of this study is to determine the relationship between adherence to HAART and the clinical situation of HIV patients seen at the Pharmacy Department of Hospital de Navarra, and to determine how to detect factors associated with a lack of adherence.

Method

This observational, descriptive transversal study examined HIV-positive patients who received their HAART at the Pharmacy Department of Hospital de Navarra in the period between February and May 2005. Inclusion criteria were as follows: adult patients infected with HIV, taking the same HAART during more than 3 months, who came to pick up their drugs during the study period, gave their informed consent and were capable of answering the questionnaire.

Table 1 Characteristics of patients included in the study

Characteristics	Patients, No.	Patients, %
Age		
30-39	50	33.6
40-49	80	53.7
Sex		
Male		69.8
Female	45	30.2
Family situation		
Living alone	22	14.8
Living with another person	120	80.6
Educational level		
Primary school	52	34.9
Secondary school	70	47
Occupation		
Employed	97	65.1
Unemployed	47	31.5
Substances consumed		
Alcohol	22	14.8
Drugs	11	7.4
Both	7	4.7
Neither	104	69.8
Psychiatric disorders		
Yes	50	33.6
No	93	62.4

We recorded socio-demographic variables (age, sex, family situation, level of studies, occupation, substance abuse, and possible psychiatric disorders), other factors that could make adherence more difficult, adverse effects experienced under the current treatment, perception of the importance of the treatment, and the relationship with the medical staff.

The SMAQ questionnaire and the drug dispensation log were used to evaluate adherence to the treatment. According to the SMAQ questionnaire, a patient was considered to be adherent to the treatment if he/she responded correctly to the 4 qualitative questions and if, in addition, answer 5 was less than or equal to 2 and answer 6 was less than or equal to 2 days. In the Pharmaceutical Treatment Programme our Pharmacy Department offers for HIV-positive patients, all dispensing was recorded, which enables us to calculate patients' adherence percentage from the relationship between drugs prescribed and drugs dispensed, keeping in mind that there is a delay before they are collected. Patients with an adherence percentage greater than or equal to 90% were considered to be adherent to the treatment according to the reviewed literature, although there are no set criteria indicating where to place the cut-off point.[2,6]

Using clinical histories in computer format, we recorded HAART characteristics (type of treatment, number of different drugs, total number of pills per day, duration of the treatment) and data about the clinical condition according to the latest analysis: viral load (number of copies/mL) and CD4+ lymphocytes (number of cells/μL). The viral load was considered undetectable when its value was less than 200 copies/mL.

Statistical analysis of the data was performed using SPSS version 14.0. Concordance between the 2 measures of adherence was evaluated using Kappa statistics and the degree of dependence between both variables was obtained using the Spearman rho coefficient. To evaluate the factors associated with the lack of adherence, the dependent variable (adherence) was compared to other independent variables using the χ^2 test, and the odds ratio (OR) was subsequently calculated for each of the factors with its confidence interval. The degree of correlation was determined by using the Kendall's tau-b coefficient. Variables with statistical significance were introduced in a logical regression model so as to identify the ones that were independently associated with poor adherence. Differences in the results were considered statistically significant, with an alpha error probability of less than 5% ($P<.05$).

Results

If we assume a potential of 80% for detecting statistical significance using a bilateral Wald test for each of the co-variables in a logistic regression model, and keep in mind that the level of significance is 5%, it is necessary to include at least 143 patients in the study. Out of the total of 606 HIV-positive patients that come to the Pharmacy Department of Hospital de Navarra to pick up their drugs, 150 were randomly selected of those who met the inclusion criteria, and 149 of these gave their consent. Table 1 shows the social and health characteristics of the participants in the study.

Out of the different HAART combinations, the most common were 2 nucleoside analogue reverse transcriptase inhibitors (NARTIs) with a non-analogue one (NNRTI) in 41.6% of all cases, followed by the group with 2 NARTIs with 1 or 2 protease inhibitors (PIs) in 32.9%.

The percentage of patients adhering to the prescribed treatment, as defined by the SMAQ questionnaire in the last 3 months, was 41.6%; however, according to the dispensation log, the percentage of adherent patients in the last 3 months reached 86.6%. The Spearman's rho coefficient was equal to 0.013 ($P=.876$). There was no concordance between the 2 measurements of adherence (kappa = 0.8%), and only 44% of the patients (66/149) were classified the same according to both methods (Table 2).

Regarding the clinical situation, 76.5% showed an undetectable viral load (<200 copies/mL) in the latest analysis, and we observed that in patients classed as adherent by either of the 2 methods, the risk of developing viral failure was less (Table 3).

As for the sociodemographic factors, the bivariate analysis resulted showed a higher percentage of non-adherent patients according to the SMAQ and in the group consisting of women, substance abusers and patients with psychiatric disorders ($P<.05$) (Table 4). For adherence that was estimated according to dispensation logs, we found

Table 2 Comparison between the 2 methods for measuring adherence

		SMAQ		Total
		Adherent, No.	Non-adherent, No.	
Logs	Adherent (n)	54	75	129
Dispensing	Non-adherent (n)	8	12	20
	Total	62	87	149

Kappa = 0.008. *P*=.875.

Table 3 Relationship between adherence and clinical situation

Method	No. of patients	Undetectable VL	
SMAQ	ADH (62)	54/62 (87%)	P=.010 OR=3.5
	Non ADH (87)	60/87 (69%)	95%CI, 1.4-9.1
Logs	ADH (129)	104/129 (80%)	P=.003 OR=4
	Non ADH (20)	10/20 (50%)	95%CI, 1.5-11

ADH indicates adherent patients; CI, confidence interval; Non ADH, non-adherent patients; OR, odds ratio; VL, viral load.

Table 4 Relationship between adherence according to the SMAQ and sociodemographic factors

	No. (%)	Adherents, No. (%)	Non-adherents, No. (%)	χ^2 (P-value)	Correlation coefficient (*P*-value)
Age					
<30	6 (4)	2 (3.2)	4 (5.6)	.056	—0.14 (.057)
30-39	50 (33.6)		32 (36.8)		
40-49	80 (53.7)	32 (51.6)	48 (55.2)		
≥50	13 (8.7)	10 (16.1)	3 (3.4)		
Sex					
Male	104 (69.8)	50 (80.6)	54 (62.1)	.015	0.199 (.10)
Female	45 (30.2)		33 (37.9)		
Family situation					
Alone	22 (14.8)	12 (19.7)	10 (11.6)	.394	0.131 (.088)
In a couple	52 (34.9)	24 (39.3)	28 (32.6)		
Friends	5 (3.3)	1 (1.6)	4 (4.7)		
Family	63 (42.3)	22 (36.1)	41 (47.7)		
Occupation					
Employed	97 (65.1)	43 (70.5)	54 (65.1)	.548	.044 (.595)
Unemployed	47 (31.5)	18 (29.5)	29 (34.9)		
Substances consumed					
Alcohol	22 (14.8)	8 (13.6)	14 (16.5)	.029	—0.152 (.50)
Drugs	11 (7.4)	0	11 (12.9)		
Both	7 (4.7)	3 (5.1)	4 (4.7)		
Neither	104 (69.8)	48 (81.4)	56 (65.9)		
Educational level					
Without any education	6 (4)	2 (3.3)	4 (4.7)	.596	—1.039 (.299)
Primary school	52 (34.9)	20 (33.3)	32 (37.2)		
Secondary school	70 (47)	28 (46.7)	42 (48.8)		
Higher education	18 (12.1)	10 (16.7)	8 (9.3)		
Psychiatric disorders					
Yes	50 (33.6)		37 (42.5)	.023	—2.793 (.005)
No	93 (62.4)	46 (74.2)			

*The Kendall's tau-b correlation coefficient was calculated because variables are codified as discreet.

no significant differences relating to any of the socio-demographic variables.

For those factors that can mean difficulty in maintaining correct adherence to treatment, nearly 80%of the patients referred to one of those listed on the questionnaire; most listed 1 or 2 factors (49%) while 26.2%indicated 3-5 factors. Table 5 includes the list of the cited difficulties by order of frequency in which we can observe that adverse effects of the drugs were the main problem indicated by the patients. Those patients who were not adherent according to the SMAQ listed more factors than the adherents did (*P*=.007). Analysing the factors one by one showed an

Table 5 Factors making adherence difficult according to patients, by frequency

Order of frequency	Factor		Patients, %	Patients, %
1	Adverse effects	Diarrhoea	26.8	38.3
		Lipodystrophy	26.2	
		Itching and spasms	17.4	
		Insomnia	14.8	
		Nausea	14.1	
		Dizziness	12.8	
		Muscle pain	12.8	
		Others	11.4	
		Agitation	7.4	
		Vomiting	6.7	
		Hallucinations		
2	Large number of capsules per dose			28.9
3	Prolonged treatment			26.2
4	Having to take several doses daily			24.2
5	Difficulty to maintain confidentiality			23.5
6	Incompatibility of doses with job situation			17.4
7	Taste or size of capsules			8.7
8	Meeting dietary requirements			8.1
9	Lack of social or family environment			5.4
10	Others			1.3

association between the adherence measured by he questionnaire and the following factors: "large number of capsules," "having to take several doses a day," "the taste or size of the capsules," "having to comply with the specific dietary requirements," and "lack of proper social or family environment" (Table 6). If we consider estimated adherence according to the dispensation logs, we only find an association with the factor of "high number of capsules per dose" (P=.025). This factor was mentioned by 25.6% of adherent patients, while 50% of non-adherent patients listed it as a problem.

On the other hand, although the association between the HAART type and adherence was not significant, a correlation was observed between the treatment type and the number of cited factors (P=.046). Likewise, a lower percentage of patients among those following the most comfortable treatment regimens (3 NARTIs or 2 NARTIs + 1 NNRTI) listed one of the factors. Patients following a regimen containing PI more commonly list at least one factor.

Out of all factors that can make adherence to the prescribed treatment more difficult, the most common factor indicated by participants in the study was adverse effects. Sixty-three point eight percent referred to an adverse effect, with those signalling 1-2 effects being most common. As shown in Table 5, the most commonly experienced adverse effects included diarrhoea and lipodystrophy. Patients not categorised as adherents by the SMAQ questionnaire listed a higher number of adverse effects (P=.026); however, after individual analysis of each effect, no statistical connection was found with adherence, although non-adherents listed effects more frequently. When using the dispensation log method, we found an association between adherence and the presence of nausea and vomiting, and non-adherent patients made more references to both effects (P<.005 for both factors).

Logistic regression

Multivariate analysis of those variables that had been associated with non-adherence in the bivariate analysis showed that lack of a proper social or family environment has a negative effect on adherence as measured by the SMAQ questionnaire (P<.05).

On the other hand, "large number of pills per dose" is a factor that is related to lack of adherence according to the dispensation log method. Patients who indicated this factor were 2.7 times less adherent that those who did not (OR=2.7; P<.05).

Discussion

The lack of concordance among different methodologies for estimating adherence to HAART has been described in many articles, both national and international. For example, Gao and Nau[7] found significant differences in how adherence was measured by the Morisky test and the test of skipped doses in the last 2 days or the last 2 weeks. Similarly, Martín et al[3] observed a low level of agreement between adherence detected using the ACTG questionnaire (AIDS Clinical Trials Group) and estimates based on dispensation logs. The study published by Ventura et al[8] also determined a minor concordance between the ESPA scale (a simplified scale for detecting adherence problems) and questionnaire-based methods. The results of that study clearly corroborate the

Table 6 Relation between adherence according to the SMAQ and factors indicated by patients

Factors indicated by patientss	No. patients	Adherent patients, No. (%)	Non-adherent patients, No. (%)	χ^2 (*P*-value)	Correlation coefficient* (P-value)
Large number of capsules					
Yes	43	12 (19.4)	31 (35.6)	.031	—0.177 (.024)
No	106	50 (80.6)	56 (64.4)		
Several doses daily					
Yes	36	9 (14.5)	27 (31)	**.02**	0.190 (.024)
No	113	53 (85.5)	60 (69)		
Prolonged treatment					
Yes	39	13 (21)	26 (29.9)	.222	—0.10 (.014)
No	110	49 (79)	61 (70.1)		
Size/taste					
Yes	13	2 (3.2)	11 (12.6)	**.045**	—0.165 (.026)
No	136	60 (96.8)	76 (87.4)		
Dietary requirements					
Yes	12	1 (1.6)	11 (12.6)	**.015**	—0.20 (.005)
No	137	61 (98.4)	76 (87.4)		
Incompatibility doses/job					
Yes	26	8 (12.9)	18 (20.7)	.217	—0.101 (.201)
No	123	54 (87.1)	69 (79.3)		
Confidentiality difficult					
Yes	35	13 (21)	22 (25.3)	.54	—0.05 (.535)
No	114	49 (79)	65 (74.7)		
Proper environment					
Yes	8	0	8 (9.2)	**.014**	—0.201 (.003)
No	141	62 (44)	79 (90.8)		
Adverse effects					
Yes	57	21 (33.9)	36 (41.4)	.353	—0.076 (.348)
No	92	41 (66.1)	51 (58.6)		

*The Kendall's tau-b correlation coefficient was calculated because variables are codified as discreet.

lack of concordance among the different methods described in the literature.

If we evaluate the SMAQ questionnaire compared to the dispensation logs, the low percentage of adherent patients could be due to the restrictive nature of some of the questions, since even patients who only occasionally skip a dose are classified as non-adherent by this method. Furthermore, the short evaluation period may have exaggerated this result, due to the fact that sporadic events that can influence adherence may have arisen in this brief interval and affected the results.

Therefore, given that adherence is a dynamic process that can change with time, its evaluation must be continuous and present during the entire duration of the treatment.

The relationship between adherence to HAART and viral suppression has been shown by numerous studies.[3,9,10] According to the test, the high percentage of patients with an undetectable viral load among non-adherents may be due in part to the sporadic skipping of some doses without clinical repercussions. However, such motives as drug interactions, resistance to antiretroviral drugs or false answers given by the patient can cause the presence of a detectable viral load in adherent patients.

We observed a higher number of non-adherents among women, which corroborates other published studies.[11,13] Some authors have related this fact with a higher rate of side effects and depression in this group,[13] in addition to prostitution and having to take care of children.[11]

The association between drug use and the presence of psychiatric disorders and low adherence has been observed in many studies,[3,9,10,13-15] although in our case the regression analysis did not corroborate this.

The fact that most factors showing a significant correlation to adherence in the bivariate analysis do not show that correlation in the multivariate analysis could be due to interrelation between the independent variables. We found that the factor that is independently associated with adherence, when measured with either the SMAQ

questionnaires or the dispensation logs, does not coincide. For this reason, we might think that the 2 methods measure different facets of reality or that the results may be random. In the SMAQ method, the factor that explains lack of adherence is the lack of a proper social and family environment; however, this factor is listed last by patients, which could occur because all those who indicate this factor are non-adherents. Having social and familial support has been associated with better adherence to HAART in other studies.[14,16] Patients who are classified as non-adherents under the dispensation log method attach more importance to aspects related with treatment complexity, such as the high number of capsules per dose.

The main limitation of this work is that it has a transversal design, which prevents us from knowing the true relationship between these factors and adherence. On the other hand, in studies of HIV-positive patients, we must consider the vast differences between patients and recall that these results cannot be applied to other populations.

Regarding the reasons that make following the treatment correctly more difficult, Stone et al[17] indicate that factors related to the difficulty of the regimen are some of the main barriers. These findings have been confirmed in other studies.[11,12,16,18] Along these lines, Trotta et al[19] showed that simplifying the treatment and adapting it to patients' schedules are strategies for improving adherence to the treatment.

Follow-up on HAART is associated with the appearance of varied and common adverse effects that can affect patients' quality of life and consequently, their adherence.[20] In this respect, we observed that patients classified as non-adherents pointed to a higher number of adverse effects, although there was no association in the regression analysis. However, in a study by Ammassari et al[18] on a cohort of 358 patients, a negative association was observed between the adverse effects that occurred and adherence to HAART. The adverse effects that our patients listed most often were diarrhoea and lipodystrophy. The latter considered to be a long-term toxic effect of HAART, is becoming extremely important because it has been linked to decreased adherence.[21,22]

Evaluation of the aspects related to quality of life, health and the satisfaction with HAART as perceived by patients is becoming increasingly important due to its relationship with adherence, and therefore with the effectiveness of the treatment.[23-25]

Conducting this study leads us to consider the possibility that the dispensation log system used in the Pharmaceutical Treatment Programme for HIV-positive patients is a viable method for evaluating patients' adherence as related to its clinical repercussions. However, it should be used in conjunction with an interview or questionnaire system to detect factors that have a negative affect on each patient's adherence, in order to propose intervention strategies for them. This interview should be given in a continuous fashion and the questions must be asked to each patient individually.

References

1. Panel de expertos GESIDA y Plan Nacional sobre el Sida. Recomendaciones de GESIDA, Plan Nacional sobre el Sida respecto al tratamiento antirretroviral en adultos infectados por el virus de la inmunodefi ciencia humana. Enf Infecc Microbiol Clin. 2007;25:32-53.
2. Recomendaciones GESIDA/SEFH/PNS para mejorar la adherencia al tratamiento antirretroviral. [Accessed June 2008] Available from: www.gesida.seimc.org
3. Martín V, Ortega L, Pérez MR, Mostaza JL, Ortiz de Urbina JJ, Rodríguez M, et al. Factores predictores de no adherencia al tratamiento antirretroviral de gran actividad. Enferm Infecc Microbiol Clin. 2002;20:491-7.
4. Knobel H. Cómo y por qué debe monitorizarse la adherencia al tratamiento antirretroviral en la actualidad. Enferm Infecc Microbiol Clin. 2002;20:481-3.
5. Knobel H, Alonso J, Casado JL, Collazos J, González J, Ruiz I, et al. Validation of a simplifi ed medication adherente questionnaire in a large cohort of HIV-infected patients: The GEEMA Study. AIDS. 2002;16:605-13.
6. Codina C, Martín M, Tuset M, del Cacho E, Ribas J. Adherencia al tratamiento antirretroviral. El Farmacéutico Hospitales. 2005;162:28-40.
7. Gao X, Nau DP. Congruente of three self-report measures of medication adherente among HIV patients. Ann Pharmacother. 2000;34:1117-22.
8. Ventura JM, Mínguez C, Fernández EM, Alós M, Andrés J. Escala simplificada para detectar problemas de adherencia (ESPA) al tratamiento antirretroviral. Farm Hosp. 2006;30:171-6.
9. Aguirrezábal A, Alvarez M, Escobar A, Teira R, Pampliega J, Pérez M, et al. Tratamiento antirretroviral. Adherencia y eficacia durante un año de seguimiento. El Farmacéutico Hospitales. 2002;130:6-13.
10. Gross R, Yip B, Lo Re III V, Wood E, Alexander CS, Harrigan PR, et al. A simple, dynamic measure of antiretroviral therapy adherence predicts failure to maintain HIV-1 supression. JID. 2006;194:1108-14.
11. Puigventós F, Riera M, Delibes C, Peñaranda M, de la Fuente L, Boronat A. Estudios de adherencia a los fármacos antirretrovirales. Una revisión sistemática. Med Clin (Barc). 2002;119:130-7.
12. Bartlett JA. Addresing the challenges of adherente. J Acquir Immune Defic Syndr. 2002;29 Suppl 1:S2-S10.
13. Riera M, de la Fuente L, Castanyer B, Puigventós F, Villalonga C, Ribas MA, et al. Adherencia a los fármacos antirretrovirales medida por la concentración de fármacos y el recuento de comprimidos. Variables relacionadas con una mala adherencia. Med Clin (Barc). 2002;119:286-92.
14. Ruiz I, Olry de Labry A, Prada JL, Rodríguez J, Causse M, López MA, et al. Impacto de los factores demográfi cos y psicosociales en la no adherencia a los fármacos antirretrovirales. Enferm Infecc Microbiol Clin. 2006;24:373-8.
15. Escobar I, Campo M, Martín J, Fernández-Shaw C, Pulido F, Rubio R. Factors affecting patient adherente to highly active antiretroviral therapy. Ann Pharmacother. 2003;37:775-81.
16. Viciana P, Rubio R, Ribera E, Knobel H, Iribarren JA, Arribas JR, et al. Estudio longitudinal de adherencia, satisfacción y efectividad del tratamiento antirretroviral administrado una vez al día, frente a dos veces al día, en una cohorte española de infectados por el VIH (estudio CUVA: cualquiera una vez al día). Enferm Infecc Microbiol Clin. 2008;26: 127-34.
17. Stone VE, Jordan J, Tolson J, Miller R, Pilon T. Perspectives on adherence and simplicity for HIV-infected patients on antiretroviral therapy: self-report of the relative importance of multiple attributes of highly active antiretroviral therapy (HAART) regimens in predicting adherence. J Acquir Immune Defic Syndr. 2004;36:808-16.

18. Ammassari A, Murri R, Pezzotti P, Trotta MP, Ravasio L, de Longis P, et al. Self-reported symptoms and medication side effects influence adherence to highly active antiretroviral therapy in persons with HIV infection. J Acquir Immune Defic Syndr. 2001;28:445-9.
19. Trotta MP, Ammasari A, Melzi S, Zaccarelli M, Ladisa N, Sighinolfi L, et al. Treatment-related factors and highly active antiretroviral threrapy adherence. J Acquir Immune Defic Syndr. 2002;31 Suppl 3:S128-S131.
20. López RM, Juárez JC. Efectos adversos del tratamiento antirretroviral. El Farmacéutico Hospitales. 2005;162:47-56.
21. Duran S, Savès M, Spire B, Cailleton V, Sobel A, Carrieri P, et al. Failure to maintain long-term adherence to highly active antiretroviral therapy: the role of lipodistrofy. AIDS. 2001;15:2441-4.
22. Heath KV, Singer JO, Shaughnessy MV, Montaner JSG, Hogg RS. Intentional nonadherence due to adverse symptoms associated with antiretroviral therapy. J Acquir Immune Defic Syndr. 2002;31:211-7.
23. Knobel H. Calidad de vida, satisfacción, adherencia y efectividad del tratamiento antirretroviral. Enf Infecc Microbiol Clin. 2005;23:579-80.
24. Condes E, Aguirrebengoa K, Dalmau D, Estrada JM, Force L, Górgolas M, et al. Validación del cuestionario de satisfacción con el tratamiento antirretroviral: cuestionario CESTA. Enferm Infecc Microbiol Clin. 2005;23:586-92.
25. Godin G, Côte J, Naccache H, Lambert L, Trottier S. Prediction of adherence to antiretroviral therapy: A one-year longitudinal study. AIDS Care. 2005;17:493-504.