

Original

## Adherence to highly active antiretroviral therapy in Spain. A meta-analysis

Carmen Ortego<sup>a,\*</sup>, Tania Bibiana Huedo-Medina<sup>b</sup>, Javier Vejo<sup>a</sup>, Francisco Javier Llorca<sup>c</sup><sup>a</sup> Departamento de Enfermería, University of Cantabria, Spain<sup>b</sup> Center for Health, Intervention, and Prevention (CHIP), University of Connecticut, USA<sup>c</sup> Group of Epidemiology and Computational Biology, University of Cantabria, Spain; CIBER de Epidemiología y Salud Pública (CIBERESP), Spain

## ARTICLE INFO

## Article history:

Received 16 April 2010

Accepted 5 October 2010

Available online 5 May 2011

## Keywords:

HAART

AIDS/HIV

Adherence

Meta-analysis

Observational studies

## ABSTRACT

**Objectives:** To estimate the percentage of adherence to highly-active antiretroviral therapy (HAART) in Spanish observational studies and to identify the variables associated with adherence.**Methods:** Seven electronic databases were used to locate the studies. Six inclusion criteria were established. Two coders codified the variables independently. Inter-coder reliability was calculated. Publication bias was analyzed through the Begg, Egger and Trim and Fill tests. Homogeneity was evaluated using the Q test and the I<sup>2</sup> index. A random effects model was assumed to estimate both the overall percentage of adherence and to explain heterogeneity.**Results:** This meta-analysis included 23 observational studies, yielding a total of 34 adherence estimates. The sample was composed of 9,931 HIV-positive individuals (72% men) older than 18 years under treatment with HAART. The percentage of patients adhering to an intake of >90% of the prescribed antiretroviral drugs was 55%. Wide heterogeneity was detected (I<sup>2</sup> = 91.20; 95%CI: 88.75–93.13). Adherence was mainly measured using a single strategy (47.8%), the most widely used being self-report (48.7%). In the univariate analysis, the following factors were significant: infection stages A ( $\beta = 0.68$ ,  $p < 0.001$ ) and B ( $\beta = -0.56$ ,  $p < 0.01$ ), viral loads >200 copies/ml ( $\beta = -0.41$ ,  $p < 0.05$ ) and <200 ( $\beta = 0.39$ ,  $p < 0.05$ ), and university education ( $\beta = -0.66$ ,  $p < 0.05$ ).**Conclusions:** The overall percentage of adherence was 55%, although this value may be an overestimate. Adherence was associated with infection stage A and with a viral load of <200 copies/ml.

© 2010 SESPAS. Published by Elsevier España, S.L. All rights reserved.

**Adherencia al tratamiento antirretroviral de gran actividad (TARGA) en España. Un metaanálisis**

## RESUMEN

**Objetivo:** Calcular el porcentaje de adherencia al TARGA en estudios observacionales españoles, así como identificar las variables asociadas a ella.**Métodos:** Para localizar los estudios se emplearon siete bases bibliográficas. Se establecieron seis criterios de inclusión. Dos codificadores realizaron la codificación de forma independiente. Se calculó la fiabilidad intercodificadores. El sesgo de publicación se evaluó mediante los tests de Begg y de Egger, y Trim & Fill. La homogeneidad se estimó mediante la prueba Q y el índice I<sup>2</sup>. Se asumió un modelo de efectos aleatorios tanto para la estimación del porcentaje global de adherencia como para explicar la heterogeneidad.**Resultados:** El metaanálisis incluyó 23 estudios observacionales que proporcionaron 34 estimaciones de la adherencia. La muestra está constituida por 9931 individuos VIH+ (72,2% hombres), mayores de 18 años y en tratamiento con TARGA. El porcentaje de pacientes con una adherencia al tratamiento de >90% de ingestión de los antirretrovirales prescritos fue del 55%. Se detectó una gran heterogeneidad (I<sup>2</sup> = 91.20; IC95%: 88.75–93.13). La adherencia fue evaluada principalmente con una única estrategia (47,8%); el autoinforme fue la más empleada (48,7%). En el análisis univariado resultaron significativo los estadios A ( $\beta = 0,68$ ,  $p < 0,001$ ) y B ( $\beta = -0,56$ ,  $p < 0,01$ ), la carga viral >200 copias/ml ( $\beta = -0,41$ ,  $p < 0,05$ ) y <200 copias/ml ( $\beta = 0,39$ ,  $p < 0,05$ ), y el nivel de educación de estudios superiores ( $\beta = -0,66$ ,  $p < 0,05$ ).**Conclusiones:** El porcentaje global de adherencia fue del 55%, pero este valor puede estar sobrestimado. La adherencia se asoció al estadio A de la infección y a una carga viral <200 copias/ml.

© 2010 SESPAS. Publicado por Elsevier España, S.L. Todos los derechos reservados.

## Palabras clave:

TARGA

Sida/VIH

Adherencia

Metaanálisis

Estudios observacionales

## Introduction

Highly active antiretroviral therapy (HAART) has improved the clinical status and prognosis of most patients infected with HIV,

decreasing their morbidity and mortality<sup>1–3</sup>. Therefore, since 1997 and coinciding with the widespread use of HAART, opportunistic infections have markedly decreased and the quality of life of HIV-infected patients has improved<sup>4</sup>.Studies of the first HAART claimed that almost perfect adherence, classically greater than 95%<sup>5,6</sup>, was required to obtain maximal effectiveness. Recent studies have suggested that therapeutic objectives can be attained at lower levels of compliance

\* Corresponding author.

E-mail address: ortegoc@unican.es (C. Ortego).

**Table 1**  
Description of the studies included in the meta-analysis.

Authors	Year	Data base	Design	Duration (weeks)	Cut-off	Number of strategies	n baseline	Type of group	Proportion of adherence			
									Baseline	Between 4-16 weeks	Between 17-26 weeks	More than 27 weeks
Abellán J et al	1999	No	L	16	>90%	1	78	A		0.82		
							86	B		0.70		
Alcoba M et al	2003	No	C		>90%	3	106		0.58			
Codina C et al	2002	No	L	52	>90%	3	96					0.83
Escobar I	2003	No	L	52	>95%	2	88		0.52		0.47	0.24
Fumaz CR et al	2008	No	C		>95%	2	87		0.62			
García de Olalla P et al	2002	Yes (table)	C		>90%	2	385	Men	0.62			
							173	Women	0.58			
Gordillo V et al	1999	No	C		>90%	2	366		0.58			
Inés SM et al	2008	No	C		>90%	1	50		0.42			
Knobel H et al.	2002	Yes <sup>a</sup>	L	52	>90%	3	3004			0.63	0.65	0.68
Knobel H et al	2004	Yes <sup>a</sup>	L	48	>90%	1	85					0.49
Ladero L et al	2005	Yes	L	52	>95%	1	80	Men	0.45			0.41
							20	Women	0.35			0.45
Martín MT et al	2007	Yes	L	26	>90%	1	1427	Men			0.69	
							509	Women			0.59	
Martín J et al	2001	Yes	C		>90%	2	155	Men	0.39			
							59	Women	0.31			
Martín V et al	2002	No	C		>90%	2	206		0.48			
Morillo R et al	2005	Yes (table)	L	12	>95%	1	85	Men	0.56			
							29	Women	0.55			
Ortega L et al	2004	No	C		>90%	3	136		0.44			
Remor E	2000	Yes (table)	L	26	>90%	1	59	Men			0.14	
							41	Women			0.15	
Riera M et al	2002	Yes	L	39	>90%	2	147	Men				0.66
							55	Women				0.39
Ruiz I et al	2006	No	C		>90%	1	320		0.88			
Tornero C et al	2005	Yes	C		>90%	1	68	Men	0.74			
							39	Women	0.72			
Ventura JM et al	2006	Yes	C		>95%	2	46	Men	0.37			
							19	Women	0.37			
Ventura JM et al	2007	No	C		>90%	1	234		0.47			
Viciano P et al	2008	No	L	26	>90%	1	611	QD			0.61	
							367	BID			0.53	

C: cross-sectional; L: longitudinal; A: conventional medical assessment; B: protocolized assessment; QD: once-daily dosing; BID: twice-daily dosing.

<sup>a</sup> Could not be used.

in regimens based on non-nucleoside analog reverse-transcriptase and protease inhibitors boosted with ritonavir, especially in patients who achieved undetectable viremia<sup>7–10</sup>.

Although viral suppression is feasible with moderate levels of adherence to HAART, several studies have shown that the emergence of resistant strains<sup>11,12</sup> and mortality<sup>13</sup> increase with lower adherence.

Although many studies have evaluated adherence to HAART and its associated variables, their results vary depending on how adherence was measured, the characteristics of the samples, and the remaining variables analyzed. A systematic review identifying and explaining these discrepancies is required to increase adherence to HAART.

In Spain, the prevalence of HIV is around three infections per thousand inhabitants<sup>14</sup>. Although the incidence of AIDS has markedly decreased since the new antiretroviral treatments began to be used, Spain remains one of the countries with the highest incidence of AIDS in Western Europe<sup>15,16</sup>. In this country, antiretroviral medicines are administered free of charge through the medical pharmacological services of the public health system. The overall annual expenditure on these medicines has been estimated to be more than a seventh of the total medical pharmacological expenditure<sup>17,18</sup>.

No meta-analyses of adherence to HAART in the Spanish population have been published. The number of studies on adherence to HAART in Spain has increased, allowing them to be systematically reviewed and to shed light on the design and improvement of studies of HAART adherence interventions.

The objective of this study was to carry out a meta-analysis of HAART adherence in Spain and to synthesize observational studies in order to estimate average adherence and identify the variables associated with this adherence.

## Methods

### Search strategy and study selection

The studies were selected from (a) seven electronic databases (PsycInfo, Medline, IME, EMI, Teseo, IBECs, ISOC and ISI Web of Knowledge) using a boolean search on the title of any type of publication: {[HAART OR highly active antiretroviral therapy] AND adheren\* AND [HIV OR AIDS OR (human immu\* virus) OR (acquired immu\* syndrome)] AND [Spanish OR Spain]}; (b) Web browsers; (c) the summary of the latest conference proceedings; (d) funded projects on HIV / AIDS in Spain and (e) tracing of references cited in others studies. The studies had to be written either in English or in Spanish.

Studies were included in the review if they (a) aimed to evaluate adherence to HAART in a Spanish sample, (b) had a cross-sectional or cohort design, (c) evaluated an HIV-positive sample over 18 years old under treatment with HAART, (d) measured adherence at least once and using one strategy, (e) established an intake of >90% or 95% of the medication prescribed as the cut-off point for adherence, and (f) provided sufficient information to obtain the proportion of adherence to HAART.

The search ended on September 13, 2009 and studies from 1998 were included. Twenty-three independent studies that met the six selection criteria were included in this meta-analysis (table 1). These 23 primary studies<sup>19–41</sup> provided 34 estimates of adherence to HAART. In three studies<sup>20,32,34</sup> the total independence among their samples could not be checked.

The authors of 21 of the 23 primary studies included in the meta-analysis were emailed to request information on the databases they had used in their studies or at least a set of data that would allow two groups to be constructed: men and

**Table 2**  
Description of the sample.

Variables	Levels	n	%	k
Sex	Man	6740	72.23	34
	Woman	2591	27.77	34
Age M (SD)		37.87 (0.826)		34
Educational level	None	295	9.85	10
	Primary	415	13.86	9
	Secondary	2139	71.44	11
	High	145	4.84	6
Employment status	Not working	500	38.88	9
	Active	786	61.12	10
Living	Alone	42	13.95	4
	With other(s)	259	86.05	4
Group	Heterosexual	2334	27.52	27
	Homosexual	1726	20.35	22
	IVDU	4420	52.12	27
Route of infection	Sexual	3596	46.3	25
	Parenteral	4072	52.43	25
	Both	99	1.27	4
E stage baseline	A	1431	35.57	15
	B	1182	29.38	15
	C	1410	35.05	15
	AIDS	1588	39.47	17
Baseline viral load	>200 copies/ml	765	43.86	20
	<200 copies/ml	979	56.14	19
End viral load	>200 copies/ml	619	31.18	10
	<200 copies/ml	1366	68.82	11
Baseline CD4	>200 cells/ml	1524	73.38	19
	<200 cells/ml	553	26.62	19
End CD4	>200 cells/ml	2061	86.13	11
	<200 cells/ml	332	13.87	11
Active IVDU	91		6	
	In methadone program	307		12
Psychiatric comorbidity	300		4	
Adverse reactions	820		9	
Naïve		974		16

n: number of subjects; k: number of studies; %: percentage of individuals; IVDU: intravenous drug user.

women. Nineteen authors responded to the message. The databases of eight studies and additional data from three studies were received.

### Coding

Two independent trained raters coded each study following the coding manual (available from the main author on request). The final coding form registered 42 variables, which were grouped into three sets: “extrinsic”, of the “design” and the “sample”.

Although no scale to assess the methodological quality was used, a small group of variables related to the methodological design were coded to compare adherence according to the studies' characteristics.

### Calculation of effect sizes and study outcomes

The proportion of adherence to HAART was estimated in each study as the effect size index. When, due to gender or location, more than one group could be drawn from a study, separate estimates of adherence were calculated for each group. If adherence was measured with more than one strategy, the average adherence was calculated. If the study evaluated adherence at different time points, the first assessment of adherence was chosen to avoid dependence, although a sensitivity analysis was performed for each set of measurements including all the possible comparisons.

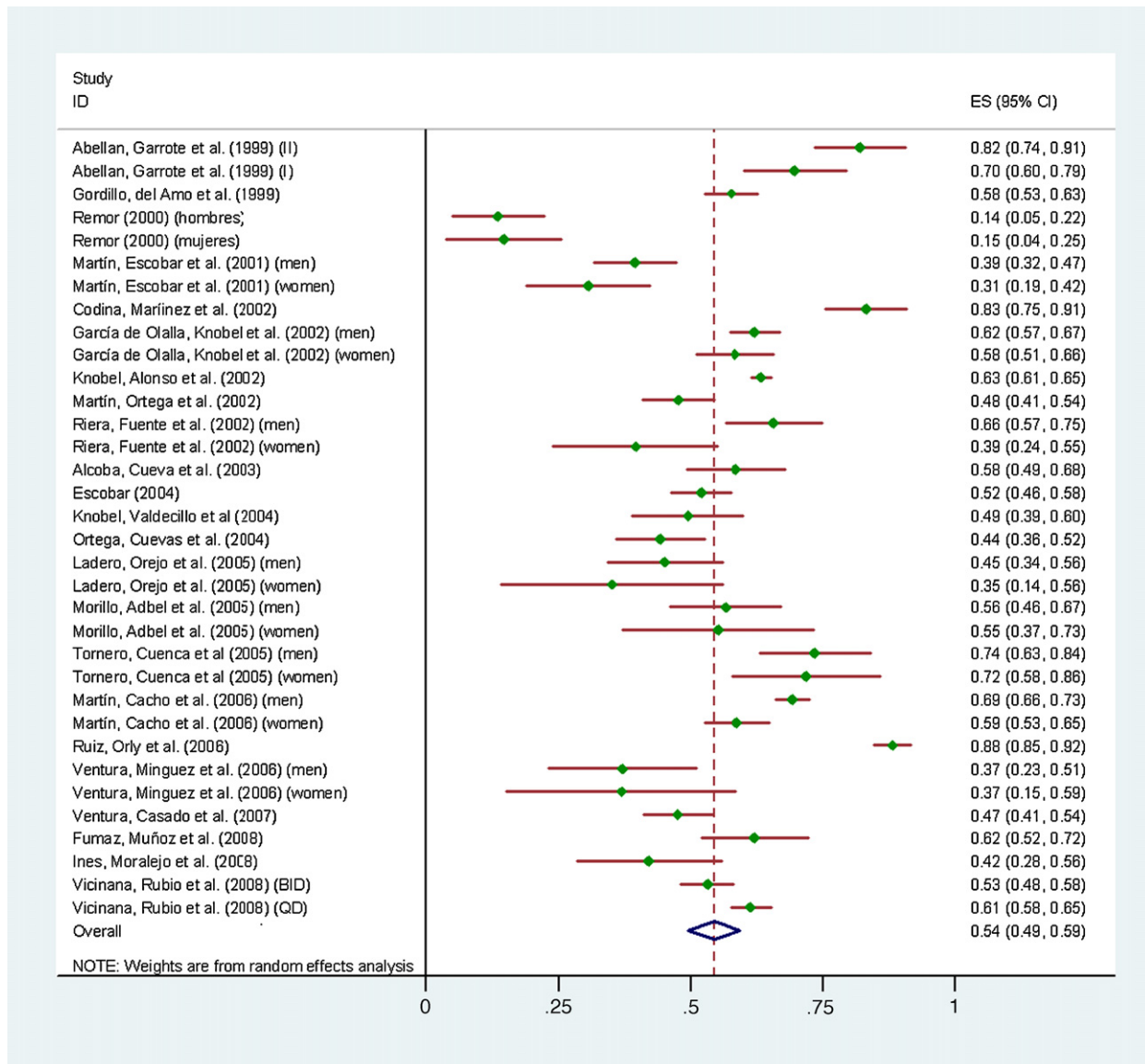


Chart 1. Forest plot.

Because the length of follow-up varied widely across studies, we divided outcomes into four measurement intervals as a strategy to examine all study assessments: between 0-3 weeks ( $k = 21$ ), between 4-16 weeks ( $k = 3$ ), between 17-26 weeks ( $k = 6$ ), more than 27 weeks ( $k = 4$ ).

To ensure the normality of the effect size index, all the statistics were obtained using a logit transformation of the proportion of adherence ( $T = \ln\left(\frac{p}{1-p}\right)$ ), where  $p$  was the proportion of adherence for each comparison. Then, the meta-analysis using a random effect model weighted by the inverse variance was performed. Finally, all the results were transformed back to a proportion for a more comprehensive interpretation of the data using the formula<sup>42</sup>  $p = \frac{e^T}{1+e^T}$ . This outcome ranges from 0 to 1, where 1 indicates that all the patients have achieved high adherence (at least >90%), while 0 indicates that no patient has exceeded this cut-off point.

Homogeneity was evaluated using the  $Q$  test and the  $I^2$  index with its confidence interval<sup>43</sup>. The relationship among study dimensions and the proportion of adherence variability was examined by using modified least squares regression analyses with weights equivalent to the inverse of the variance for each effect size. When feasible factors related significantly to the proportion of adherence, they were entered into a series of models

controlling for intercorrelations among the maintained study dimensions. These combined models allowed determination of the extent to which variation might be exclusively attributed to surviving study dimensions or not. The continuous variables that were significant in the univariate analyses were zero-centered to reduce multicollinearity<sup>44</sup>; if they were categorical, dummy variables were created<sup>44</sup>. Models with simultaneous independent variables were created if these factors were registered in more than five studies ( $k > 5$ ) and under mixed-effects assumptions, which are considered to have more conservative statistical power<sup>45</sup>.

The publication bias was analyzed through three different strategies: Trim and Fill<sup>46</sup>, Begg's strategy<sup>47</sup>, and the Egger test<sup>48</sup>.

## Results

### Study and adherence characteristics, and sample

The characteristics of the 23 primary studies were as follows: 21 (91.3%) studies were published and two (8.7%) were unpublished (doctoral theses), 10 (43.5%) were written in English and 13 (56.5%)

in Spanish, 12 (52.2%) had a cross-sectional design and 11 (47.8%) a longitudinal design. All of the studies were performed between 1998 and 2008.

Patients with an intake of >90% of prescribed HAART were considered adherent. Adherence was assessed using just one strategy in 11 studies (47.8%), two strategies in eight (34.8%) and three strategies in four (17.4%). Self-report was the most frequently used strategy to quantify adherence in 19 studies (48.7%), followed by registration of dispensing medicines in 11 (28.2%), plasma drug concentration in four (10.3%), counting of surplus medication in two (5.1%), viral load in two (5.1%) and electronic devices in one (2.6%).

From the 23 studies included in table 1, a sample (table 2) composed of 9,331 HIV-positive patients older than 18 years under HAART was obtained, with 6,740 (72.2%) men and 2,591 (27.8%) women and a mean age of 37.9 years (SD: 2.83, range: 33-44).

#### Overall adherence to HAART

The average adherence to HAART under the random effects model for the Spanish sample was 0.54 (95%CI: 0.49-0.59), showing wide heterogeneity ( $I^2 = 91.20$ ; 95%CI: 88.75-93.13) under the fixed-effects model. Therefore, only the results under the random-effects model and mixed-effects model to explain the heterogeneity not explained by the model ( $I^2 = 51\%$ ; 95%CI: 11.45-72.88) are presented. Chart 1 shows the forest plot of the proportion of adherence of the 34 groups as well as the overall mean proportion of adherence (at the bottom of the chart). Chart 2 shows the proportion of adherence by sex.

A sensitivity analysis was performed to (i) test the influence of possible outliers, (ii) test the patterns of the set of studies divided by the week of measurement, and (iii) determine whether the results were affected by the exclusion of some studies in which the total independence among their samples could not be checked. Comparison of all the possible outliers revealed that none worked as a real outlier. The time interval showed the same patterns when the data were analyzed by interval as a separate meta-analysis rather than as a moderator without inclusion of more than one measurement per study. Finally, we decided to maintain all studies with a likely dependence because their exclusion did not affect the final results but would involve a substantial loss of information.

Intercoder reliability was higher than 0.90. Cohen's kappa was used for categorical variables ( $\kappa = 0.98$ ) and the Spearman-Brown correlation coefficient for continuous variables ( $r = 0.955$ ). Disagreements were solved through discussion.

The three tests used to assess possible publication bias aimed to show absence of bias. These tests were the Trim and Fill (the results indicate that there are no missing studies), Begg's test ( $z = -0.10$ ,  $p = 0.922$ ) and Egger's test (bias = -1.58,  $t = -1.98$ ,  $p = 0.054$ ).

#### Factors modifying adherence to HAART

A higher percentage of participants in stage A and with baseline viral load <200 copies/ml showed greater adherence. However, lower adherence was found when a higher percentage of patients were in stage B, with a baseline viral load >200 copies/ml, and with a high level of education, that is, education from secondary school onwards (table 3; this table depicts the variables registered in more than five groups,  $k > 5$ ).

Some of the significant moderators showed high collinearity ( $r_s > 0.90$ , e.g., stage A and stage B, the two variables for baseline viral load) and therefore separate combined models were tested by different groups of moderators, avoiding dependence among them and excluding high educational level due to the small number of studies reporting this data ( $k = 6$ ). After all the possible combinations of stage and baseline viral load, the only

**Table 3**  
Univariate analysis. Mixed effects model.

Variables	Proportion of adherence	IC95%	$\beta$
<b>Study design</b>			
<i>Design</i>			
Longitudinal ( $k = 18$ )	0.56	0.5-0.62	-0.023
Cross-sectional ( $k = 16$ )	0.55	0.49-0.61	
<i>Screening interval (weeks)</i>			
Between 0 - 3 ( $k = 21$ )	0.54	0.6-0.76	0.05
Between 4 - 16 ( $k = 3$ )	0.72	0.83-0.94	
Between 17 - 26 ( $k = 6$ )	0.47	0.59-0.38	
More than 27 ( $k = 4$ )	0.61	0.74-0.82	
<i>Cut-off for adherence</i>			
>95% ( $k = 8$ )	0.49	0.39-0.58	0.26
>90% ( $k = 26$ )	0.57	0.52-0.62	
<i>N° of strategies (<math>k = 34</math>)</i>			
One ( $k = 18$ )	0.57	0.63-0.89	0.01
Two ( $k = 12$ )	0.5	0.58-0.5	
Three ( $k = 4$ )	0.63	0.74-0.87	
<b>Sample characteristics</b>			
<i>% Men (<math>k = 34</math>)</i>			
0	0.49	0.41-0.58	0.18
100	0.59	0.53-0.65	
<i>% Women (<math>k = 34</math>)</i>			
0	0.59	0.53-0.65	-0.18
100	0.49	0.4-0.58	
<i>Mean year (<math>k = 34</math>)</i>			
32	0.48	0.38-0.58	0.2
44	0.64	0.53-0.73	
<i>% High educational level (<math>k = 6</math>)</i>			
9	0.68	0.4-0.87	-0.66 <sup>a</sup>
37	0.16	0.04-0.48	
<i>% Working (<math>k = 10</math>)</i>			
34	0.36	0.17-0.62	0.48
64,37	0.65	0.5-0.78	
<i>% Currently active IVDU (<math>k = 6</math>)</i>			
27	0.63	0.54-0.72	0.13
78	0.56	0.47-0.65	
<i>% Methadone (<math>k = 12</math>)</i>			
2	0.53	0.32-0.73	-0.52
18	0.59	0.32-0.82	
<i>% Stage A (<math>k = 15</math>)</i>			
15	0.29	0.21-0.38	0.68 <sup>b</sup>
55	0.79	0.66-0.88	
<i>% Stage B (<math>k = 15</math>)</i>			
8	0.72	0.55-0.84	-0.56 <sup>c</sup>
46	0.33	0.24-0.44	
<i>% Baseline viral load &gt; 200 copies/ml (<math>k = 20</math>)</i>			
10	0.59	0.47-0.7	-0.41 <sup>a</sup>
100	0.3	0.17-0.48	
<i>% Baseline viral load &lt; 200 copies/ml (<math>k = 19</math>)</i>			
0	0.3	0.16-0.5	
80	0.59	0.46-0.72	
<i>% Adverse reactions (<math>k = 9</math>)</i>			
14	0.54	0.41-0.66	0.21
45	0.6	0.5-0.72	

IVDU = intravenous drug user.

<sup>a</sup>  $p < 0.05$ .

<sup>b</sup>  $p < 0.001$ .

<sup>c</sup>  $p < 0.01$ .

For categorical variables with more than one category, the value is not  $\beta$  but the  $r$  multiple of the regression model.

variable that remained significant when baseline viral load (> 200 copies/ml because this value was measured in the largest number of studies) was controlled for was the percentage of patients in stage A. The model explaining 52% of the variance, more than expected by chance, was stage A ( $\beta = 0.69$ ,  $p = 0.0005$ ) controlling by baseline viral load > 200 copies /ml ( $\beta = -0.21$ ,  $p = 0.30$ ), yielding the following regression equation (expressed in the unstandardized coefficients, the B values):  $-1.637 + 0.060 \times (\text{stage A}) - 0.0078 (\text{baseline viral load} > 200 \text{ copies/ml})$ .

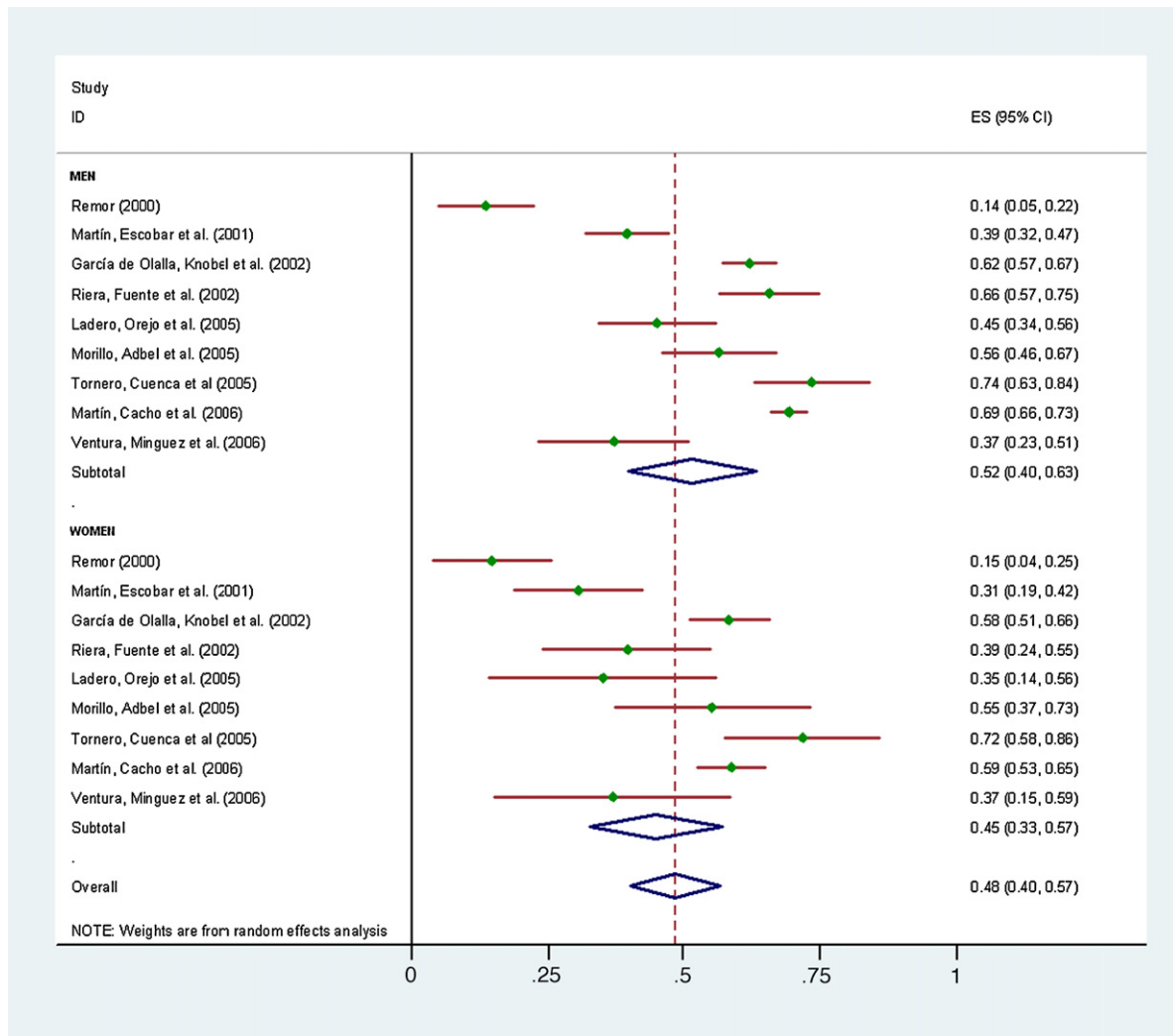


Chart 2. Forest plot.

## Discussion

The main result of this study is that adherence to HAART in Spain is 55%. This percentage is similar or slightly lower than that found by other authors in individuals from different populations worldwide<sup>49–55</sup>. However, in this meta-analysis, this value could be overestimated for two reasons: firstly, adherence was assessed by a single strategy in more than half of the primary studies and secondly, because the most widely used strategy was self-report.

When the variable of baseline viral load < 200 copies/ml was controlled for, the higher the percentage of patients in stage A, the greater the adherence. Other studies have also found lower adherence in patients with high viral loads than in those with low loads<sup>56,57</sup>. The stage of infection was closely related to the viral load, indicating the importance of controlling for this variable in the final model. In this meta-analysis, the higher percentage of subjects in stage A, the greater the adherence, whereas the higher percentage of subjects in stage B, the lower the adherence. Similarly, several authors found greater adherence in patients with a shorter time since infection<sup>58–60</sup>. Quality of life<sup>61</sup>, degree of distress<sup>62</sup> and patients' expectations of treatment could be determining variables in these results.

Although the level of education was significant, this variable was only registered in six studies. Thus, more research is needed to enable generalizations related to this moderator to be made.

This meta-analysis also codified other variables that several studies have found to be associated with higher adherence: male gender<sup>63–67</sup>, older age<sup>68–72</sup>, having a stable job<sup>58,59,73</sup>, not having adverse reactions<sup>50,63,66,73–76</sup>, not consuming illegal drugs<sup>53,65,66,76–79</sup>, not drinking alcohol<sup>53,65,74,79</sup>, not having psychiatric comorbidity<sup>49,50,53,77,78,80</sup> and having some support<sup>49,58,78</sup>. Although all these variables were significant in the univariate level and under a fixed effects model, they lost their significance in order to assume a random effects model.

One of the limitations of this study is the small number of variables registered in the primary studies. Spanish studies assessing adherence to HAART are generally highly restrictive in the number of variables analyzed, often limited to recording the most common demographic, biological or pharmacological variables, without recording those that seem to play a role of equal or greater weight in the adherence to HAART, such as psychosocial variables. Although this meta-analysis codified 42 variables, most could not be used in the multivariate analysis given the small percentage of studies that recorded them, which significantly restricted the analysis of heterogeneity.

Another limitation is the wide heterogeneity of this meta-analysis. The small number of studies identified to form part of this meta-analysis also played a decisive role in these limitations.

Adherence to the HAART in Spanish samples should continue to be assessed in order to determine variability and improve

adherence. However, adherence should be measured by more than one strategy to avoid its overestimation and follow experts recommendations<sup>81</sup>. Assessments of adherence should record a larger number of variables because, although many of the variables codified in this meta-analysis were significant, the small number of studies that recorded them prevented this model from being employed as an explanatory model. Finally, stage A and viral baseline load < 200 copies/ml were significantly associated with higher adherence, whereas stage B and viral baseline load > 200 copies/ml were associated with lower adherence. Therefore, programs aimed at maintaining and increasing adherence should be aware of both patients' stage of infection and their viral baseline load.

Adherence to HAART should be approached from multidisciplinary, multifactorial and biopsychosocial perspectives. Greater collaboration among researchers would help to gain further knowledge and reduce duplication of efforts<sup>82</sup>.

### Author contributions

C. Ortego and T.B. Huedo-Medina conceptualized the study, analyzed the data, and led the writing of the manuscript. J. Vejo assisted with the acquisition and content coding. F.J. Llorca assisted with the conceptualization of the study and the data interpretations. Every author provided valuable critical revisions of the manuscript and also agreed in both contents and form of the final version, being C. Ortego the responsible of this article.

### Funding/support

Project financed by IFIMAV. N/Ref.: PSG 10/02

### Conflicts of interest

The authors indicate no conflicts of interest.

### Acknowledgments

We thank study authors who made their data available for this study. Juan Botella who assisted in advising statistically and revising the coding manual, Julia del Amo for their assessment in the search of epidemiological information, and Soledad Fernandez for reviewing the English translation.

### References

- Hogg RS, Heath KV, Yip B, et al. Improved survival among HIV-infected individuals following initiation of antiretroviral therapy. *JAMA*. 1998;279:450-4.
- Mocroft A, Ledergerber B, Katlama C, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet*. 2003;362:22-9.
- Palella Jr FJ, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med*. 1998;338:853-60.
- Santos E, Fuertes A. Efectos adversos de los fármacos antirretrovirales. *Fisiopatología, manifestaciones clínicas y tratamiento*. *An Med Intern*. 2006;23:338-44.
- Carpenter CC, Cooper DA, Fischl MA, et al. Antiretroviral therapy in adults: updated recommendations of the International AIDS Society-USA Panel. *JAMA*. 2000;283:381-90.
- Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med*. 2000;133:21-30.
- Bangsberg DR, Acosta EP, Gupta R, et al. Adherence-resistance relationships for protease and non-nucleoside reverse transcriptase inhibitors explained by virological fitness. *AIDS*. 2006;20:223-31.
- Bangsberg DR. Less than 95% adherence to nonnucleoside reverse-transcriptase inhibitor therapy can lead to viral suppression. *Clin Infect Dis*. 2006;43:930-41.
- Lima VD, Harrigan R, Murray M, et al. Differential impact of adherence on long-term treatment response among naive HIV-infected individuals. *AIDS*. 2008;22:2371-80.
- Martin M, Del Cacho E, Codina C, et al. Relationship between adherence level, type of the antiretroviral regimen, and plasma HIV type 1 RNA viral load: a prospective cohort study. *AIDS Res Hum Retroviruses*. 2008;24:1263-8.
- Bangsberg DR, Charlebois ED, Grant RM, et al. High levels of adherence do not prevent accumulation of HIV drug resistance mutations. *AIDS*. 2003;17:1925-32.
- Harrigan PR, Hogg RS, Dong WW, et al. Predictors of HIV drug-resistance mutations in a large antiretroviral-naive cohort initiating triple antiretroviral therapy. *J Infect Dis*. 2005;191:339-47.
- Lima VD, Harrigan R, Bangsberg DR, et al. The combined effect of modern highly active antiretroviral therapy regimens and adherence on mortality over time. *J Acquir Immune Defic Syndr*. 2009;50:529-36.
- Ministerio de Sanidad y Consumo. *Plan multisectorial frente a la infección por VIH y el sida. España 2008-2012*. Madrid: Ministerio de Sanidad y Consumo, Centro de Publicaciones; 2008.
- Instituto de Salud Carlos III. *Vigilancia epidemiológica del sida en España. Registro Nacional de casos de sida. 2009 Informe semestral n° 1. Año 2009*; 1.
- WHO Regional Office for Europe. *HIV/AIDS surveillance in Europe 2008*. Geneva; 2009.
- Quiros R. Políticas farmacéuticas: su repercusión en la prestación farmacéutica. *Revista Administración Sanitaria*. 2008;6:633-9.
- Tornero C, Cuenca A, Santamaría A, et al. Distribución del gasto farmacéutico en medicación antirretroviral. *An Med Intern*. 2004;21:269-71.
- Abellán J, Garrote M, Pulido F, et al. Evaluation of adherence to a triple antiretroviral therapy in HIV-positive patients. *Eur J Intern Med*. 1999;10:202-5.
- Alcoba M, Cuevas MJ, Pérez-Simón MR, et al. Assessment of adherence to triple antiretroviral treatment including indinavir: role of the determination of plasma levels of indinavir. *J Acquir Immune Defic Syndr*. 2003;33:253-8.
- Codina C, García F, Gatell JM, et al. Comparación de tres métodos de cálculo de adherencia en pacientes con tratamiento antirretroviral. *Enferm Infecc Microbiol Clin*. 2002;20:484-90.
- Escobar I. *Desarrollo y evaluación de un programa de intervención para la mejora de la adherencia al tratamiento antirretroviral en pacientes con infección VIH: determinación del perfil del paciente incumplidor en un área de salud*. Dpto. Farmacia y Tecnología Farmacéutica. Universidad Complutense de Madrid; 2003.
- Fumaz CR, Muñoz-Moreno JA, Molto J, et al. Sustained antiretroviral treatment adherence in survivors of the pre-HAART era: attitudes and beliefs. *AIDS Care*. 2008;20:796-805.
- García de Olalla P, Knobel H, Carmona A, et al. Impact of adherence and highly active antiretroviral therapy on survival in HIV-infected patients. *J Acquir Immune Defic Syndr*. 2002;30:105-10.
- Gordillo V, Del Amo J, Soriano V, et al. Sociodemographic and psychological variables influencing adherence to antiretroviral therapy. *AIDS*. 1999;13:1763-9.
- Ines SM, Moralejo L, Marcos M, et al. Adherence to highly active antiretroviral therapy in HIV-infected inmates. *Curr HIV Res*. 2008;6:164-70.
- Knobel H, Alonso J, Casado JL, et al. Validation of a simplified medication adherence questionnaire in a large cohort of HIV-infected patients: the GEEMA study. *AIDS*. 2002;16:605-13.
- Knobel H, Vallecillo G, Guelar A, et al. Simplified therapy with zidovudine, lamivudine, and abacavir for very nonadherent, treatment-failing patients. *HIV Clin Trials*. 2004;5:65-73.
- Ladero Martín L, Orejudo Hernández S, Carrobes Isabel J, et al. Consumo de drogas y adherencia a la terapia antirretroviral de pacientes en programa de mantenimiento con metadona. *Adicciones*. 2005;17:203-14.
- Martín MT, Del Cacho E, López E, et al. Reacciones adversas del tratamiento antirretroviral. Relación entre los síntomas percibidos y el cumplimiento terapéutico. *Med Clin*. 2007;4:127-33.
- Martín J, Escobar I, Rubio R, et al. Study of the validity of a questionnaire to assess the adherence to therapy in patients infected by HIV. *HIV Clin Trials*. 2001;2:31-7.
- Martín Sánchez V, Ortega Valín L, Pérez Simón MR, et al. Factores predictores de no adherencia al tratamiento antirretroviral de gran actividad. *Enferm Infecc Microbiol Clin*. 2002;20:491-7.
- Morillo R, Abdel L, Márquez E, et al. Análisis de las causas de suspensión del régimen antirretroviral simplificado abacavir, lamivudina y zidovudina. *Farm Hosp*. 2005;29:164-70.
- Ortega L, Cuevas MJ, Pérez R, et al. Factores predictores de carga viral detectable en pacientes en tratamiento antirretroviral de gran actividad. *Med Clin*. 2004;123:45-9.
- Remor E. *Infección por VIH y sida: características psicológicas y adhesión al tratamiento*. Dpto. Psicología Biológica y de la Salud. Universidad Autónoma Madrid; 2000.
- Riera M, La Fuente L, Castanyer B, 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*. 2002;119:286-92.
- Ruiz I, Orly A, Prada JL, et al. Impacto de los factores demográficos y psicosociales en la no adherencia a los fármacos antirretrovirales. *Enferm Infecc Microbiol Clin*. 2006;24:373-8.
- Tornero C, Cuenca A, Nolasco A, et al. Gasto farmacéutico en medicación antirretroviral y posibilidades de optimización. *An Med Intern*. 2005;22:575-8.
- Ventura Cerdá J, Mínguez Gallego C, Fernández Villalba E, et al. Escala simplificada para detectar problemas de adherencia (ESPA) al tratamiento antirretroviral. *Farm Hosp*. 2006;30:171-6.
- Ventura Cerdá JM, Casado Gómez MA, Escobar Rodríguez I, et al. Preferencias, satisfacción y adherencia con el tratamiento antirretroviral: estudio ARPAS (II). *Farm Hosp*. 2007;31:340-52.
- Viciana P, Rubio R, Ribera E, 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 CUYA: cualquiera una vez al día). *Enferm Infecc Microbiol Clin*. 2008;26:127-34.
42. Lipsey MW, Wilson D. *Practical meta-analysis*. London: Sage; 2001.
  43. Huedo T, Sánchez-Meca J, Marín F, et al. Assessing heterogeneity in meta-analysis: Q statistic or I<sup>2</sup> index? *Psychol Meth*. 2006;11:193-206.
  44. Aiken LS, West SG. *Multiple regression: testing and interpreting interactions*. Newbury Park, CA: Sage; 1991.
  45. Hedges L, Pigott TD. The power of statistical tests in meta-analysis. *Psychol Meth*. 2001;3:203-17.
  46. Duval S, Tweedie R. Trim and Fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;455-63.
  47. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;4:1088-101.
  48. Egger M, Davey G, Schneider M, et al. Bias in meta-analysis detected by a simple graphical test. *BMJ*. 1997;315:629-34.
  49. Buathong N, Hiransuthikul N, Tangwongchai S, et al. Association between depression and adherence to highly active antiretroviral therapy among adult HIV infected patients in Thailand. *Asian Biomed*. 2009;3:127-33.
  50. Carrieri MP, Lepout C, Protopopescu C, et al. Factors associated with nonadherence to highly active antiretroviral therapy: a 5-year follow-up analysis with correction for the bias induced by missing data in the treatment maintenance phase. *J Acquir Immune Defic Syndr*. 2006;41:477-85.
  51. Heckman BD, Catz SL, Heckman TG, et al. Adherence to antiretroviral therapy in rural persons living with HIV disease in the United States. *AIDS Care*. 2004;16:219-30.
  52. Mills EJ, Nachega JB, Buchan I, et al. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. *JAMA*. 2006;296:679-90.
  53. Protopopescu C, Raffi F, Roux P, et al. Factors associated with non-adherence to long-term highly active antiretroviral therapy: a 10 year follow-up analysis with correction for the bias induced by missing data. *J Antimicrob Chemother*. 2009;63:599-606.
  54. Puigventós F, Riera M, Delibes C, et al. Estudios de adherencia a los fármacos antirretrovirales. *Med Clin*. 2002;119:130-7.
  55. Rudy BJ, Murphy DA, Harris DR, et al. Adolescent Trials Network for HIV/AIDS Interventions. Patient-related risks for nonadherence to antiretroviral therapy among HIV-infected youth in the United States: a study of prevalence and interactions. *AIDS Patient Care STDS*. 2009;23:185-94.
  56. D'Arminio Monforte A, Lepri AC, Rezza G, et al. Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients I. CO. N. A. Study Group. Italian Cohort of Antiretroviral-Naive Patients. *AIDS*. 2000;14:499-507.
  57. Mocroft A, Youle M, Moore A, et al. Reasons for modification and discontinuation of antiretrovirals: results from a single treatment centre. *AIDS*. 2001;15:185-94.
  58. Carballo E, Cadarso-Suárez C, Carrera I, et al. Assessing relationships between health-related quality of life and adherence to antiretroviral therapy. *Qual Life Res*. 2004;13:587-99.
  59. Estévez C. Variables psicosociales asociadas a la adhesión terapéutica en pacientes con infección por el VIH en tratamiento antirretroviral de alta eficacia. 2000.
  60. Remor E. Valoración de la adhesión al tratamiento antirretroviral en pacientes VIH+. *Psicothema*. 2002;14:262-7.
  61. Penedo FJ, González JS, Dahn JR, et al. Personality, quality of life and HAART adherence among men and women living with HIV/AIDS. *J Psychosom Res*. 2003;54:271-8.
  62. Remor E, Ulla S, Arranz P, et al. ¿Es la percepción de control un factor protector contra el estrés emocional en personas VIH+? *Psiquis*. 2001;22:111-6.
  63. Arrondo A, Sainz ML, Andrés EM, et al. Factores relacionados con la adherencia en pacientes infectados por el virus de la inmunodeficiencia humana. *Farm Hosp*. 2009;14-11.
  64. Floridia M, Giuliano M, Palmisano L, et al. Gender differences in the treatment of HIV infection. *Pharmacol Res*. 2008;58:173-82.
  65. Kumar V, Encinosa W. Effects of antidepressant treatment on antiretroviral regimen adherence among depressed HIV-infected patients. *Psychiatr Q*. 2009;80:131-41.
  66. Robison LS, Westfall AO, Mugavero MJ, et al. Short-term discontinuation of HAART regimens more common in vulnerable patient populations. *AIDS Res Hum Retroviruses*. 2008;24:1347-55.
  67. Turner BJ, Laine C, Cosler L, et al. Relationship of gender, depression, and health care delivery with antiretroviral adherence in HIV-infected drug users. *J Gen Intern Med*. 2003;18:248-57.
  68. Brañas F, Berenguer J, Sánchez-Conde M, et al. The eldest of older adults living with HIV: response and adherence to highly active antiretroviral therapy. *Am J Med*. 2008;121:820-4.
  69. Carrieri P, Cailleton V, Le Moing V, et al. The dynamic of adherence to highly active antiretroviral therapy: results from the French National APROCO cohort. *J Acquir Immune Defic Syndr*. 2001;28:232-9.
  70. Horne R, Cooper V, Gellaity G, et al. Patients' perceptions of highly active antiretroviral therapy in relation to treatment uptake and adherence: the utility of the necessity-concerns framework. *J Acquir Immune Defic Syndr*. 2007;45:334-41.
  71. ¿Son adherentes los pacientes VIH+ de edad avanzada? Pasquau J, editor. *XII Congreso Nacional sobre Sida, "Una mirada al Mediterráneo"*. Organizado por SEISIDA, 20-22 mayo. Valencia. 2009.
  72. Schneider J, Kaplan SH, Greenfield S, et al. Better physician-patient relationships are associated with higher reported adherence to antiretroviral therapy in patients with HIV infection. *J Gen Intern Med*. 2004;19:1096-103.
  73. Ammassari A, Murri R, Pezzotti 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.
  74. Chesney MA, Ickovics JR, Chambers DB, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials. The AACTG adherence instruments. Patient Care Committee & Adherence Working Group of the Outcomes Committee of the adult. *AIDS Care*. 2000;12:255-66.
  75. Cooper V, Gellaity G, Hankins M, et al. The influence of symptom experiences and attributions on adherence to highly active anti-retroviral therapy (HAART): a six-month prospective, follow-up study. *AIDS Care*. 2009;21:520-8.
  76. Roca B, Gómez CJ, Arnedo A. Stavudine, lamivudine and indinavir in drug abusing and non-drug abusing HIV-infected patients: adherence, side effects and efficacy. *J Infect*. 1999;39:141-5.
  77. Cruess DG, Minor S, Antoni MH, et al. Utility of the Millon Behavioral Medicine Diagnostic (MBMD) to predict adherence to highly active antiretroviral therapy (HAART) medication regimens among HIV-positive men and women. *J Pers Assess*. 2007;89:277-90.
  78. Malta M, Strathdee SA, Magnanini MM, et al. Adherence to antiretroviral therapy for human immunodeficiency virus/acquired immune deficiency syndrome among drug users: a systematic review. *Addiction*. 2008;103:1242-57.
  79. Moatti JP, Carrieri MP, Spire B, et al. Adherence to HAART in French HIV-infected injecting drug users: the contribution of buprenorphine drug maintenance treatment. The Manif 2000 study group. *AIDS*. 2000;14:151-5.
  80. Kalichman SC, Rompa D, DiFonzo K, et al. HIV treatment adherence in women living with HIV/AIDS: research based on the information-motivation-behavioral skills model of health behavior. *J Assoc Nurses in AIDS Care*. 2001;12:58-67.
  81. Panel de expertos de la Secretaría del Plan Nacional sobre Sida (SPNS), Sociedad Española de Farmacia Hospitalaria (SEFH), Grupo de Estudio del Sida (GESIDA). Mejorar la adherencia al tratamiento antirretroviral. Recomendaciones de SPNS/SEFH/GESIDA. *Farm Hosp*. 2008;52:349-57.
  82. Simoni JM, Frick P, Pantalone DW, et al. Enhancing antiretroviral adherence: review of an emerging field. In: Trafton JA, Gordon W, editors. *Best practices in behavioral management of chronic disease*. 2nd ed Los Altos, CA: Institute for Disease Management; 2006. p. 70-95.