ADHERENCE TO HIGHLY ACTIVE ANTIRETROVIRAL THERAPHY (HAART) IN SPAIN. A META-ANALYSIS

C. Ortego[a], T.B. Huedo-Medina[b], J. Vejo[a] and J. Llorca[c]

[a]Departamento de Enfermería. University of Cantabria, Spain.; [b]Center for Health, Intervention, and Prevention (CHIP), University of Connecticut, USA;[c]Group of Epidemiology and Computational Biology, University of Cantabria, Spain, and CIBER Epidemiología y Salud Pública (CIBERESP), Spain

Mª Carmen Ortego Maté

Departamento de Enfermería.

Universidad de Cantabria

Avda. de Valdecilla s/n. 39008

Santander

ortegoc@unican.es

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AUTHOR CONTRIBUTIONS

C. Ortego and TB. Huedo-Medina conceptualized the study, analyzed the data, and led the writing of the manuscript. J. Vejo assisted with the acquisition and content coding. FJ. 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.

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The authors indicate no conflicts of interest.

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 dicha adherencia.

Métodos: Para localizar los estudios se emplearon siete bases bibliográficas. Se establecieron 6 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^2. Se asumió un modelo de efectos aleatorios tanto para la estimación del porcentaje global de adherencia como para explicar la heterogeneidad.

Resultados: Este metanálisis lo integran veintitrés estudios observacionales que proporcionaron treinta y cuatro 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 adherentes a una ingesta >90% de los antirretrovirales prescritos fue del 55%. Se detectó una elevada heterogeneidad (I^2 = 91.20; 95% *IC*. 88.75-93.13). La adherencia fue evaluada principalmente con una única estrategia (47.8%), siendo el autoinforme la estrategia más empleada (48.7%). En el análisis univariante resultaron significativas: los estadios A (β=0,68, p<0.001) y B (β=-0.56, p<0.01), las cargas virales >200 copias/ml (β=-0,41, p<0.05) y <200 (β=0,39, p<0.05) y los estudios superiores (β=-0,66, p<0.05).

Conclusiones: El porcentaje global de adherencia fue de 55%, no obstante este valor puede estar sobrestimado. La adherencia se asoció al estadio A de la infección y a una carga viral <200 copias/ml.

Palabras clave: TARGA, SIDA/VIH, adherencia, metaanálisis, estudios observacionales

ADHERENCE TO HIGHLY ACTIVE ANTIRETROVIRAL THERAPHY (HAART) IN SPAIN. A META-ANALYSIS

ABSTRACT

Objectives: To estimate the adherence percentage to HAART in observational studies Spanish samples, as well as identify the variables associated with such adherence.

Methods: Seven Spanish and Anglo electronic databases were used to locate the studies. Six inclusion criteria were established. Two coders codified independently. Intercoder reliability was obtained. The publication bias was analysed through the *Begg, Egger,* and *trim & fill* tests. Homogeneity was evaluated using Q test and the index I^2. A random effects model was assumed for both the global percentage estimation and to explain the heterogeneity.

Results. This meta-analysis is integrated by twenty-three observational studies, yielding a total of thirty-four adherence estimates. The sample is formed by 9931 HIV+ (72% men), older than 18 and following a treatment with HAART.

The percentage of patients adherent to an intake >90% of the prescribed antiretrovirals was 55%. A strong heterogeneity was detected (I^2 = 91.20; 95% *CI*. 88.75-93.13). Adherence was measured mainly using a single strategy (47.8%), being the self-report (48.7%) the most widely used. In the univariate analysis were significative: stages A (β=0,68, p<0.001) and B (β=-0.56, p<0.01), the viral loads >200 copies/ml (β=-0,41, p<0.05) and <200 (β=0,39, p<0.05) and the high educational level (β=-0,66, p<0.05).

Conclusions. The global adherence percentage was 55%, though such value may have been overestimated. Adherence was associated to the infection stage A and to a viral load of <200 copies/ml.

Key Words: HAART, AIDS/HIV, adherence, meta-analysis, observational studies

INTRODUCTION

The highly active antiretroviral therapy (HAART) has improved the clinical situation and the prognosis of most patients infected with HIV decreasing its morbidity and mortality (1-3). Therefore, since 1997 and coinciding with the widespread use HAART, the opportunistic infections have decreased considerably and the quality of life of patients infected with HIV has improved (4).

Studies of the first highly active antiretroviral therapies claimed that the maximum effectiveness requires almost a perfect adherence, classically greater than 95% (5,6). Recent studies suggest that at lower levels of compliance the therapeutic objectives can be attained in regimens based on reverse transcriptase non analogues of nucleoside and protease inhibitors boosted with ritonavir, especially with patients who achieved undetectable viremias (7-10).

Although the viral suppression is possible with moderate levels of adherence to HAART several studies have shown that the emergence of resistant strains (11,12) and the mortality (13) increase with the decrease of the adhesion.

In spite of the many studies that have evaluated the adherence to HAART and the variables associated with such adherence there is no unanimity in the results, which vary depending on how the adherence has been measured, on the characteristics of the samples and other variables analyzed in each study. A systematic review that identifies and explains those discrepancies is needed for increasing adherence to HAART.

In Spain the HIV prevalence is around three infections per thousand inhabitants, (14). Although there has been an important decrease in the AIDS incidence from the start of the new antiretroviral treatments Spain keeps being one of the countries with the highest incidence of AIDS in Western Europe (15,16).

In this country with a public health system antiretroviral medicines are administered free of charge through the medical pharmacological services. It has been estimated that the global annual expense in these medicines reaches more than a seventh of the total medical pharmacological expense (17,18).

In the literature there is not any meta-analysis focused on the adherence to HAART with Spanish population. The increase in the number of studies on HAART adherence in Spain allows reviewing them systematically and shedding light on the design and improvement of studies focused on HAART adherence interventions.

The objective of this study is to carry out a meta-analysis on HAART adherence in Spain synthesizing observational studies in order to estimate the average of adherence as well as identify the variables associated with such 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 conferences books; (d) funded projects on HIV / AIDS in Spain and (e) the tracing of references cited in others studies. The studies had to be written either in English or in Spanish.

The 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 cohorts design, (c) evaluated a sample over 18 years old, HIV+ in treatment with HAART, (d) measured adhesion 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 the adhesion, 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 integrated in this meta-analysis. These twenty-three primary studies (19-41) provided thirty-four estimates of the adherence to HAART. In three studies (20,32,34) it was not possible to check the total independence among their samples.

----------Table 1, about here----------

Authors of twenty-one of the twenty-three primary studies included in the meta-analysis, were emailed requesting them the databases they had used in their studies or at least a set of data that would allow the building of two groups: men and women. Nineteen authors responded to the message. The database of eight studies and additional data from three studies were received.

CODING

Two independent trained raters coded each study following the coding manual (available on request to the main author). The final coding form registered forty-two variables. These being 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 the adherence performance under those characteristics of the studies.

CALCULATION OF EFFECT SIZES AND STUDY OUTCOMES

The proportion of adherence to HAART was estimated in each study as the effect size index. When more than one group due to gender or location could be drawn from a study, separate estimates of the adherence was calculated for each group. If the adherence was measured with more than one strategy an average of adherence was calculated. If the study had evaluated the adherence at different time points the first assessment of the adherence was chosen to avoid dependence, although a sensitivity analysis was performed for each set of measurement including all the possible comparisons. Because the timing of follow-ups varied widely across studies, we divided outcomes into 4 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 the 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 transform back to a proportion for a more comprehensive interpretation of the data using the formula $p = \frac{e^T}{1+e^T}$ (42) . This outcome ranges from 0 to 1, where 1 indicates that all the patients have reached a high adherence, at least >90%, while 0 means that no patient has exceeded this cut-off point.

The homogeneity was evaluated using Q test and the index I^2 with its confidence interval (43). The relation among study dimensions and the adherence proportion variability was examined 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 adherence proportion, they were entered into a series of models controlling for

intercorrelations among the maintained study dimensions. These combined models permit a determination of the extent to which variation may be uniquely or not attributed to surviving study dimensions. The continuous variables that had been significant in the univariate analyses were zero-centered in order to reduce multicollinearity (44), if they were categorical, dummy variables were created (44). Models with simultaneous independent variables were created if those factors were registered in more than five studies ($k > 5$) and under mixed-effects assumptions that are considered to have more conservative statistical power (45).

The publication bias was analyzed through three different strategies, trim and fill (46), Begg's strategy (47), and Egger test (48).

RESULTS

STUDY, ADHERENCE DETAILS AND SAMPLE

The characteristics of the twenty-three primary studies were as follows: 21 (91.3%) studies were published and 2 (8.7%) unpublished (doctoral thesis), 10 (43.5%) written in English and 13 (56.5%) in Spanish, 12 (52.2%) had a cross-sectional design and 11 (47.8%) a longitudinal one. All of them had been performed between 1998 and 2008.

The patients who intake >90% of HAART prescribed were considered adherent. The adherence was assessed using just one strategy in 11 studies (47.8%), two strategies 8 (34.8%) and three strategies 4 (17.4%). The self-report was the most often used strategy to quantify the adherence 19 (48.7%), followed by the registration of dispensing medicines 11 (28.2%), plasma drug concentration 4 (10.3%), the counting of surplus medication 2 (5.1%), viral load 2 (5.1%) and electronic devices 1 (2.6%).

From the twenty-three studies included in table 1 a sample (table 2) formed by 9331 patients older than 18 years and HIV+ under HAART was obtained. Being 6740 (72.2%) men and 2591 (27.8%) women, with a mean age of 37.9 years (*SD*: 2.83, range: 33-44 years old)..

--------Table 2, about here----------

OVERALL ADHERENCE TO HAART

The average adherence to HAART under random effects model for a Spanish sample was .54 (95% *CI*: .49 .59) showing a large heterogeneity (I^2 = 91.20; 95% *CI*. 88.75-93.13) under fixed-effects model. Therefore only results under random-effects model and mixed-effects model to explain the heterogeneity that is 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 thirty-four groups as well as the overall mean proportion of adherence (at the bottom of the chart), and Chart 2 the proportion of adherence by sex.

----------Chart 1, about here----------

----------Chart 2, about here----------

Sensitivity analysis was performed in order to: 1/ test the influence of possible outliers, 2/ test the patterns of the set of studies divided by the week of measurement, and 3/ find out if the exclusion of some studies in which it was not possible to check the total independence among their samples affected the results. After comparing all the possible outliers it was seen that none worked as a real outlier. The interval time showed the same patterns analyzing the data by interval as separate meta-analysis than being a moderator without including more than one measurement per study. And finally it was decided to maintain all studies with a likely dependence because their exclusion did not affect the final results, but it would involve a relevant loss of information.

The intercoders reliability was higher than .90. The Cohen Kappa was used for the categorical variables ($\kappa = .98$) and Spearman-Brown correlation coefficient for the continuous variables ($r = .955$) Disagreements were solved through discussion.

The three strategies used to assess possible publication bias agreed to show absence of bias. These tests were the Trim and Fill (the results indicate that there is no study missing), the test of Begg ($z = -0.10$, $p = .922$) and the test of Egger (*bias* = -1.58, $t = -1.98$, $p = .054$).

MODIFIER FACTORS OF ADHERENCE TO HAART

A higher percentage of participants in stage A and with baseline viral load < 200 copies/ml larger adherence. However, lower adherence was showed when a higher percentage of patients were in stage B, with baseline viral load >200 copies/ml, and with a high level of education, that is, education from Secondary onwards (Table 3. This table depicts the variables that have been registered in more than 5 groups, $k>5$).

----------Table 3, about here----------

Some of the significant moderators showed high collinearity (rs > .90, e.g., stage A and stage B, the two variables for baseline viral load), so 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 with stage and baseline viral load, the only variable that remains significant controlling for the baseline viral load (being this one > 200 copies/ml because it is measured in a larger number of studies) was the percentage of patients in stage A. The model explains 52% of the variance, more than expected by chance, was Stage A ($\beta = 0.69$, $p = .0005$) controlling by baseline viral load > 200 cells/ml ($\beta = -0.21$, $p = .30$) resulting the

following regression equation (expressed in the unstandardized coefficients, the B values). -1.637 + 0.060 x (Stage A) -0.0078 (baseline viral load > 200 copies/ml).

DISCUSSION

The main result of this study shows that adherence to HAART in Spain is 55%. This percentage is similar or slightly lower than that found by other authors and referred to individuals from different populations worldwide (49-55). However, in this meta-analysis this value can be overestimated due to two reasons: First, the fact that adherence was assessed by a single strategy in more than half of the primary studies and also because the self-report was the most used strategy.

The higher percentage of patients in stage A controlling by the baseline viral load < 200 cells/ml the greater adherence. Regarding the viral load some studies have also found a lower adherence in patients with high viral loads as compared to these low loads (56,57).The stage of the infection is closely related to the viral load that is why controlling for that variable was very important in the final model. The stage of the infection is closely related to the viral load. 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. In this sense, several authors find a better adherence in those patients with a shorter time from infection (58-60). The quality of life (61), the degree of distress (62) and the patient expectations from treatment can be determining variables in these results.

Although the level of education was significant, this variable was only registered in 6 studies. Thus, more research is needed to conclude some generalizations related to this moderator.

There are other variables codified in this meta-analysis that several studies have found associated with a better adherence: being a man (63-67), being older (68-72) , having a stable job (58,59,73), not showing adverse reactions (50,63,66,73-76), not consuming illegal drugs (53,65,66,76-79), not drinking alcohol (53,65,74,79), not presenting psychiatric comorbidity (49,50,53,77,78,80) and having some support (49,58,78).Although at the univariate level and under a fixed effects model all the above variables were significant, they lost their significance in order to assume a random effects model.

LIMITATIONS

One of the limitations of this study is the small number of variables registered in the primary studies. The Spanish studies that assess adherence to HAART are generally very restrictive in the number of variables analyzed, limited in many cases to record the most common demographic, biological or pharmacological variables, forgetting variables that seem to play a role of equal or greater weight in the adherence to HAART, as the psychosocial ones. Although in this meta-analysis forty-two variables were codified most of them could not be used in the multivariate analysis given the small percentage of studies that recorded them, which significantly restricted the analysis of the heterogeneity.

The high heterogeneity of the current meta-analysis poses another limitation. The small number of studies that could be gathered to integrate this meta-analysis has also played a decisive role in these limitations.

CONCLUSIONS

It is important to continue assessing the adherence to the HAART in Spanish samples in order to get to know their variability and improve the adhesion. However, the adherence should be measured by more than one strategy in order to avoid overestimating adherence and follow experts'recommendations (81). In the assessments of the adherence it would be advisable to record a larger number of variables because though many of the variables codified in this meta-analysis were significant, the small number of studies that record them prevented this from being employed as an explanatory model. Finally it should be highlighted that stage A and viral baseline load < 200 copies/ml are associated to a significative higher adherence, whereas stage B and viral baseline load > 200 copies/ml are associated to a lower adherence. Therefore, in the programs aimed at maintaining and increasing adherence it is essential to be aware of both the patients' stage of infection and their viral baseline load.

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

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

Authors	Year	Data base	Design	Duration (weeks)	cutoff	number of strategies	*n* basal	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		.82		
							86	B		.70		
Alcoba M. et al.	2003	No	C		>90%	3	106		.58			
Codina C. et al.	2002	No	L	52	>90%	3	96					.83
Escobar I.	2003	No	L	52	>95%	2	88		.52		.47	.24
Fumaz CR. et al.	2008	No	C		>95	2	87		..62			
García de Olalla P. et al.	2002	Yes (table)	C		>90%	2	385	Men	.62			
							173	Women	.58			
Gordillo V. et al	1999	No	C		>90%	2	366		.58			
Inés SM. et al	2008	No	C		>90	1	50		.42			
Knobel H.et al.	2002	Yes*	L	52	>90%	3	3004			.63	.65	.68
Knobel H. et al.	2004	Yes*	L	48	>90%	1	85					.49
Ladero L. et al.	2005	Yes	L	52	>95%	1	80	Men	.45			.41
							20	Women	.35			.45
Martín MT. et al.	2007	Yes	L	26	>90%	1	1427	Men			.69	
							509	Women			.59	
Martín J. et al.	2001	Yes	C		>90%	2	155	Men	.39			
							59	Women	.31			
Martín V. et al.	2002	No	C		>90%	2	206		.48			
Morillo R. et al.	2005	Yes (table)	L	12	>95%	1	85	Men	.56			
							29	Women	.55			
Ortega L et al.	2004	No	C		>90%	3	136		.44			
Remor E.	2000	Yes (table)	L	26	>90%	1	59	Men			.14	
							41	Women			.15	
Riera M. et al.	2002	Yes	L	39	>90%	2	147	Men				.66
							55	Women				.39

Ruiz I. et al.	2006	No	C		>90%	1	320		.88	
Tornero C. et al.	2005	Yes	C		>90%	1	68	Men	.74	
							39	Women	.72	
Ventura JM. et al.	2006	Yes	C		>95%	2	46	Men	.37	
							19	Women	.37	
Ventura JM et al.	2007	No	C		>90 %	1	234		.47	
Viciana P. et al.	2008	No	L	26	>90%	1	611	QD		.61
							367	BID		.53

* Could not be used

C: cross-sectional L: longitudinal A: Convenctinal medical assessment B:Protocolized assessment QD:Once-daily dosing BID:twice-daily dosing

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 (.826)		34
Educational level				
	Without studies	295	9.85	10
	Primary	415	13.86	9
	Secondary	2139	71.44	11
	High	145	4.84	6
Employment status				
	Does not work	500	38.88	9
	Active	786	61.12	10
Living				
	Alone	42	13.95	4
	Accompanied	259	86.05	4
Group				
	Heterosexual	2334	27.52	27
	Homosexual	1726	20.35	22
	UDVI	4420	52.12	27
Infection way				
	Sexual	3596	46.3	25
	Parenterally	4072	52.43	25
	Both	99	1.27	4
Estage basaline				
	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 UDVI		91		6

In methadone program	307	12
Psychiatric comorbidity	300	4
Adverse reactions	820	9
Naive	974	16

n = number of subjects *k* = number of studies

% percentage of individuals

Table 3. Univariate analysis. Mixed effects model

Variables	Porportion of adherence	IC 95%		β
Design of studies				
Design				-0.023
Longitudinal (k = 18)	.56	.5	.62	
Cross-sectional (k = 16)	.55	.49	.61	
Screening interval (weeks)				0.05
Between 0 - 3 (k = 21)	.54	.6	.76	
Between 4 – 16 (k = 3)	.72	.83	.94	
Between 17 - 26 (k = 6)	.47	.59	.38	
More of 27 (k = 4)	.61	.74	.82	
Cut-off adherence				0,26
>95% (k=8)	.49	.39	.58	
>90% (k=26)	.57	.52	.62	
Nº of strategies (k=34)				0,01
One (k=18)	.57	.63	.89	
Two (k=12)	.5	.58	.5	
Three (k=4)	.63	.74	.87	
Sample characteristics				
% Men (k=34)				0,18
0	.49	.41	.58	
100	.59	.53	.65	
% Women (k=34)				-0,18
0	.59	.53	.65	
100	.49	.4	.58	
Mean year (k=34)				0,2
32	.48	.38	.58	
44	.64	.53	.73	
% High educational level (k=6)				-0,66***
9	.68	.4	.87	
37	.16	.04	.48	
% Working (k=10)				0,48
34	.36	.17	.62	
64,37	.65	.5	.78	
% Currently active UDVI (k=6)				0,13
27	.63	.54	.72	
78	.56	.47	.65	
% Methadone (k=12)				-0,52
2	.53	.32	.73	
18	.59	.32	.82	
% Stage A (k=15)				0,68**
15	.29	.21	.38	
55	.79	.66	.88	
% Stage B (k=15)				-0,56*
8	.72	.55	.84	
46	.33	.24	.44	
% Baseline viral load > 200 copies/ml (k=20)				-0,41***
10	.59	.47	.7	
100	.3	.17	.48	
% Baseline viral load < 200 copies/ml (k=19)				0,39***

0	.3	.16	.5	
80	.59	.46	.72	
% Adverse reactions (*k*=9)				0,21
14	.54	.41	.66	
45	.6	.5	.72	

*p<.01, **p<.001, ***p<.05

Note: Categorical variables with more than one category, the value is not β but the R multiple of regression model

Chart 1. Forest plot.

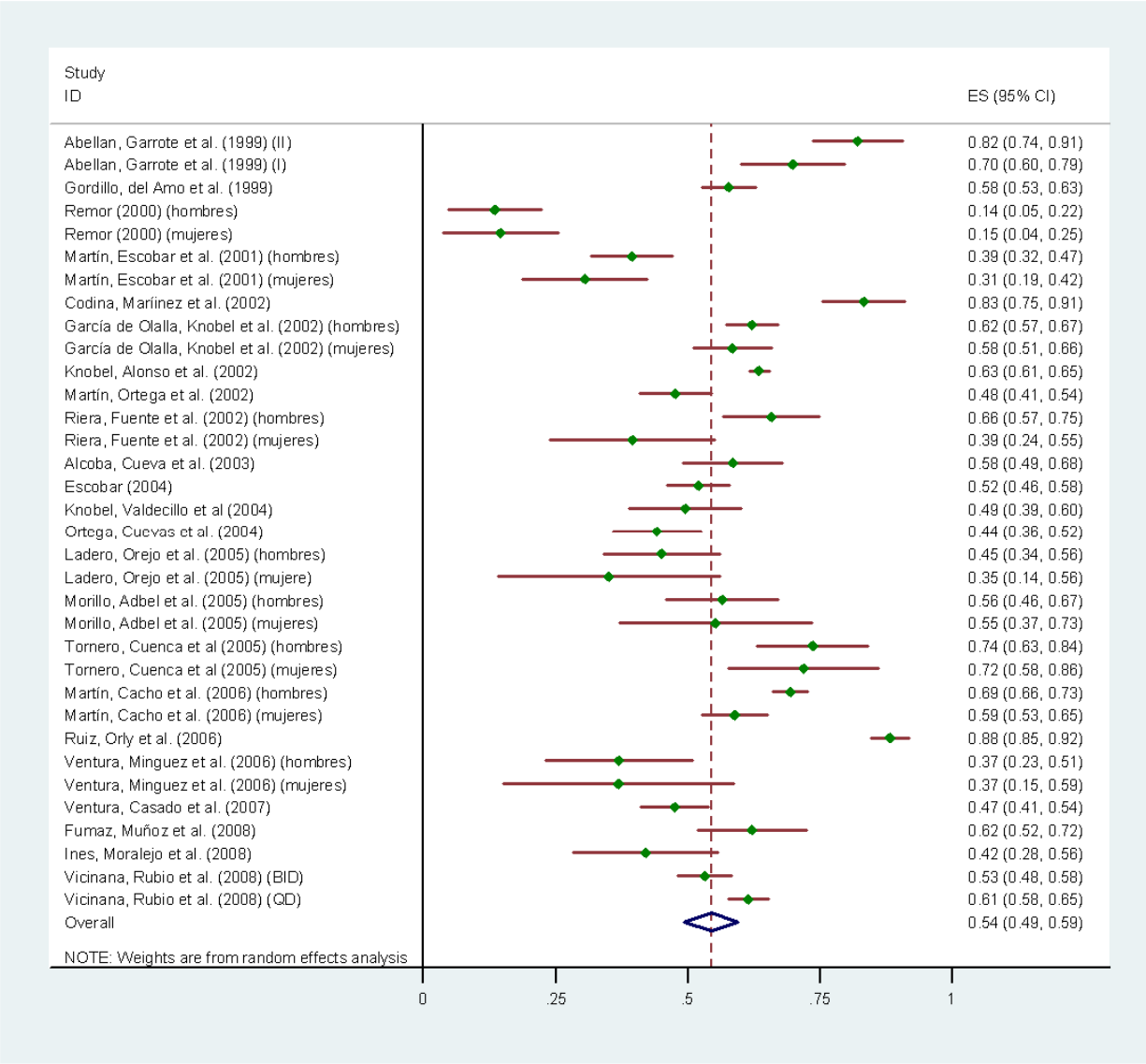

Chart 2. Forest plot.