Preferences, satisfaction and compliance with antiretroviral treatment: ARPAS study (II)

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Objective: To describe the ARPAS study and analyse the sociodemographic and clinical characteristics and patient preferences with regards the antiretroviral treatment (ART), as well as the relationship between compliance and satisfaction with the ART and quality of life.

Method: The ARPAS study has looked at adult patients diagnosed with HIV and on ART, using a protocol including sociodemographic, clinical, therapeutic and quality of life variables. Compliance was estimated using the SMAQ questionnaire; satisfaction was measured using the ESTAR questionnaire, as was quality of life with the MOS-HIV Health Survey, and treatment preferences were determined using a questionnaire prepared based on the consensus of an expert team in the field of therapeutic monitoring.

Resumen

Objetivo: Describir el estudio ARPAS y analizar las características sociodemográficas, clínicas y las preferencias de los pacientes con el tratamiento antirretroviral (TAR), así como la relación entre la adherencia y la satisfacción con el TAR y la calidad de vida.

Método: El estudio ARPAS ha evaluado a pacientes adultos, diagnosticados de infección por VIH y con TAR, mediante un protocolo que incluye variables sociodemográficas, clínicas, terapéuticas y de calidad de vida. La adherencia se estimó mediante el cuestionario SMAQ, la satisfacción mediante el cuestionario ESTAR, la calidad de vida mediante el MOS-HIV y las preferencias con el tratamiento se determinaron mediante un cuestionario elaborado a partir del consenso de un equipo experto en el seguimiento terapéutico de estos pacientes. Se realizó un análisis univariante estratificado en función de la adherencia y un análisis de regresión logística para estudiar la asociación de las variables independientes con la adherencia.

Resultados: Se evaluaron 234 pacientes (73,7% varones; 43,2 ± 7,8 años). El tiempo medio desde el diagnóstico y desde el inicio del TAR fue, respectivamente, de 10,1 ± 5,7 y 7,4 ± 4,4 años. El régimen terapéutico de dos tomas diarias (bid) se dio en el 71% de los pacientes, y el de una toma (qd) en el 21%. El 47,3% de los pacientes cumplieron criterios de adherencia según el SMAQ. El porcentaje de los pacientes con qd adherentes al TAR fue mayor que el resto de esquemas posológicos (55,3 vs. 46,5 ± 9,7, p = 0,001) y calidad de vida (81,6 ± 10,7 vs. 75,7 ± 11,8, p < 0,001) en los pacientes adherentes respecto de los no adherentes. Los modelos multivariante confirmaron la existencia de una asociación significativa entre adherencia y satisfacción, y adherencia y calidad de vida.

Conclusiones: Los pacientes consideran prioritario tratarse con un TAR potente, duradero y bien tolerado y, dentro de las preferencias entre las diferentes pautas, destacan los regímenes de una toma diaria. El estudio ARPAS demuestra la relación directa entre adherencia y satisfacción con el TAR, y entre adherencia y calidad de vida, de forma que las estrategias de mejora de la adherencia deben incluir necesariamente aspectos que permitan mejorar la satisfacción del paciente con su tratamiento e incrementar la calidad de vida.


Summary

Objective: To describe the ARPAS study and analyse the sociodemographic and clinical characteristics and patient preferences with regards the antiretroviral treatment (ART), as well as the relationship between compliance and satisfaction with the ART and quality of life.

Method: The ARPAS study has looked at adult patients diagnosed with HIV and on ART, using a protocol including sociodemographic, clinical, therapeutic and quality of life variables. Compliance was estimated using the SMAQ questionnaire; satisfaction was measured using the ESTAR questionnaire, as was quality of life with the MOS-HIV Health Survey, and treatment preferences were determined using a questionnaire prepared based on the consensus of an expert team in the field of therapeutic monitoring.

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of these patients. A stratified univariate analysis according to compliance and a logistic regression analysis were carried out to study the association of the independent variables with compliance.

**Results:** A total of 234 patients were evaluated (73.7% male; 43.2 ± 7.8 years of age). The average time since diagnosis and from the initiation of ART was 10.1 ± 5.7 and 7.4 ± 4.4 years respectively. The therapeutic regimen of twice-daily doses (bid) was applied to 71% of the patients, and once daily (qd) in 21%. A total of 43% of the patients fulfilled compliance criteria according to the SMAQ. The percentage of the patients with qd complying with the ART was greater than the remaining dosing schedules (55.3 vs. 45.1%), although not significantly (p = 0.251). No differences were observed in the sociodemographic and clinical variables in terms of compliance. An elective preference was observed for the simplest of the therapeutic regimens which contrasts with the evaluation of the ART characteristics, where power is given preference over durability, tolerance and lastly, the convenience of taking the ART. The univariate analysis showed the highest score on the satisfaction scales (50.4 ± 7.8 vs. 46.5 ± 9.7, p = 0.001) and quality of life (81.6 ± 10.7 vs. 75.7 ± 11.8, p < 0.001) in compliant patients with respect to non-compliers. The multivariate models confirm the existence of a significant association between compliance and satisfaction, and between compliance and quality of life.

**Conclusions:** Patients consider treatment with a powerful, long-lasting and well-tolerated ART a priority and among their preferences for different treatment regimes, once-daily dosing regimes are highlighted. The ARPA S study showed a direct relationship between compliance and satisfaction with ART, and between compliance and quality of life, in a manner that the strategies improving compliance must necessarily include aspects that allow them to improve patient satisfaction with treatment and quality of life.

**Key words:** Patient compliance. Patient satisfaction. Preferences. Antiretroviral therapy. Health-related quality of life. Acquired immunodeficiency syndrome. HIV. Outcome assessment.

**INTRODUCTION**

Current antiretroviral treatments (ART) are the basis for appropriate virological and immunological control of patients infected by the human immunodeficiency virus (HIV), to the point that they have changed the natural history of the disease, considerably increasing survival and giving way to a “chronification” of this infection. However, even today, poor compliance with ART is one of the main factors in treatment failure and in the selection of viral resistance. The AIDS Study Group (GESIDA), belonging to the Spanish Society of Infectious Diseases and Clinical Microbiology, in its most recent consensus document, defines compliance with antiretroviral treatment (ART) of patients infected by the human immunodeficiency virus (HIV) as the “capacity of the patient to be correctly involved in the choice, initiation and control of the ART that allows strict compliance with this, in order to achieve an appropriate suppression of viral replication”, in a manner that poor compliance is not exclusively a certain percentage of doses omitted. Compliance, also known as adherence, in the short and long term, is the result of a complex process that is developed through different stages: Acceptance of the diagnosis, perception of the need to take the treatment correctly, motivation to do so, willingness and acquisition of abilities to carry this out, the ability to overcome barriers and difficulties that may appear, and maintaining these achievements over time.

In addition to demographic and psychosocial factors, there are many other clinical and therapeutic factors involved in compliance with ART. Among these factors, it is worth pointing out the patients’ perception of health, clinical status, the relationship with the healthcare environment, and treatment schedules, referring to number of doses, number of pharmaceutical forms, tolerability and requirements for administration. Although there is a postulation that certain personal or humanistic factors, such as satisfaction with treatment, relative preferences and health-related quality of life (HRQL) perceived by the patient have an influence on compliance, these relationships have not been clearly established.

Strategies for improving compliance with ART, given their multifactorial nature, necessarily imply knowledge of influential factors and the manner in which they exercise that influence. In general terms, it is accepted that the most effective strategies are those that motivate and modify daily habits. However, since little is known about the relationship between compliance and the humanistic factors or variables based on motivational strategies, the strategies for improving compliance may not be as effective as might be desired.

Both perceived satisfaction and patient preferences are very ambiguous variables that must be clearly defined if they are to be useful in practical care or in health outcome assessment. Consequently, patient satisfaction can be considered in its relationship with the healthcare system in general, with healthcare professionals, with specific care processes, with hospital in-patient services and, furthermore, with the treatment taken by the patient. Likewise, preferences must be confined to specific conceptual areas, such as treatments, care, etc. The main problem with these “patient-centred” variables is that there are few validated instruments for measuring them. In general terms, the surveys or questionnaires usually employed are based on bibliographic reviews, on earlier or pilot-type surveys and on meetings of experts.

The relationship between compliance, satisfaction with ART and preferences is not totally defined, although they are necessarily independent variables. Some studies show a direct relationship between satisfaction and compliance with ART: The most satisfied patients are more compliant. Similarly, the relationship existing between satisfaction with the treatment and certain dimensions of HRQL, such as the physical and psychological functioning, should also be evaluated, as well as...
the equally direct relationship between HRQL and compliance with the ART\(^{16}\).

One of the key factors to be analysed, both in studies on preferences and those on satisfaction with ART, is the number of daily administrations, a field where there have been important advances and where new contributions are foreseeable in the short to medium term. A recent European survey involving 504 patients infected with HIV, of whom 87\% had received antiretroviral treatment, showed that those surveyed preferred a single daily dose (qod), and they considered a maximum of three pharmacetical forms to be ideal. However, these preferences were not contrasted with compliance\(^{17}\). Furthermore, another (telephone) survey, assessing the attributes of the ART, showed there is a preference (89\% of HIV+ patients) for twice-daily treatments (bid) as opposed to qod, as long as it provides more effective viral suppression, immune response and durability of the ART\(^{15}\), i.e., more value is placed on efficacy than on the convenience of the ART.

The ARPAS study (antiretroviral patients adherence and satisfaction) is a multicentre study driven by the Spanish Hospital Pharmacy Foundation (FEFH, Fundación Española de Farmacia Hospitalaria), the main objective of which is to determine the relationship between satisfaction and compliance with the ART in patients diagnosed with HIV. The following are among its secondary objectives: Determining the psychometric properties of a satisfaction scale regarding the ART using a validated quality of life questionnaire as a pattern for HIV+ patients, determining the preferences and expectations of the patients according to the treatment regimes, describing sociodemographic and clinical variables, and determining their relationship with patient compliance and satisfaction.

This second article describes the ARPAS study methods, the sociodemographic and clinical characteristics of the patients, as well as their preferences with regard to ART regimes and the relationship between compliance, satisfaction and HRQL.

**METHOD**

An observational, cross-sectional, multicentre study conducted between May and July 2005 in the outpatient units (OPU) of hospital pharmacy departments in 32 Spanish hospitals. Patients were included by competitive recruitment, with a minimum of 200 evaluable patients. The study was closed the week in which 15\% of this figure was exceeded (230 patients). The patients included fulfilled the following inclusion criteria: Adult patients, over 18 years of age, both sexes, diagnosed HIV+ and with stable ART during at least, the last six months at the same centre, who gave their written informed consent and were capable of understanding and answering the questionnaires.

The evaluation of the patients included was carried out cross-sectionally by using a standard protocol for gathering data which included sociodemographic variables (age, gender, educational level and employment status), clinical variables (time passed since diagnosis of the HIV infection, concomitant infection with hepatitis B and/or C, CD4 T-lymphocyte count and plasma viral load (–PVL–), therapeutic variables (time passed from the beginning of medication, number of treatments since initiation and during the last year, and therapeutic regimen) and quality of life. Compliance with ART was measured using the Spanish version of the Simplified medication adherence questionnaire (SMAQ)\(^{25}\), which classifies the patients as compliant or non-compliant. Furthermore, compliance was assessed as a continuous variable by calculating the dispensing record (DR) of antiretroviral drugs at each pharmacy department to each patient during the period (over six months) immediately before their recruitment. This variable became categorical on the basis of two cutoff-points; compliant if DR \(\geq\) 90\% and DR \(\geq\) 95\%. The patient preferences were determined using a questionnaire, the questions of which were established based on the consensus of an expert team in the therapeutic monitoring of the HIV+ patient (Appendix 1). The survey of preferences was designed with questions with response categories except for the first and fourth questions, which involved answering based on a scale. The contents of the survey aim to establish the preferences of the patients on ART in accordance with the personal and clinical situation of each patient. Consequently, questions 1-4 are non-comparative self-evaluation questions. Questions 5-8 put the patient in specific situations and intend to determine their preferences in said situations, regardless of whether the patient is experiencing them or not. In questions 2, 3, 6 and 9 there was only an option for response, and in question 10, there was a limit of three answers, listed in order of relative importance.

Patient satisfaction with the ART was measured using the ART satisfaction scale (ESTAR, escala de satisfacción con el TAR)\(^{30}\), introduced in Spain as part of the ARPAS study, based on the original English-language scale, the HIV treatment satisfaction questionnaire (HIVTSQ), designed by Woodcock et al. in 2001\(^{23}\). The ESTAR consists of 10 questions answered on a Likert scale of 0 to 6: 0 (not at all satisfied)-6 (very satisfied). In the process for validating the ESTAR, two subscales or main components were identified: Overall clinical satisfaction and satisfaction with lifestyle. The satisfaction with lifestyle subscale includes questions on the demands of the ART, its convenience and flexibility, adaptation to lifestyle and satisfaction with the knowledge on HIV infection, while the clinical satisfaction subscale analyses the ART effectiveness, side effects, overall satisfaction and satisfaction with continuing the treatment. Both subscales were analysed in accordance with the scores obtained from all the ESTAR questions, in a manner that the scores of each subscale are adjusted by the score...
weight of each question (0 to 6 points) according to the coefficients obtained for each main components in the previous psychometric analysis.

The patients’ perception of HRQL was estimated by using the Spanish version of the Medical outcomes study hiv health survey (MOS-HIV)\(^2\), which consists of 35 questions grouped into 11 dimensions: a) General health perception; b) Pain; c) Physical functioning; d) Role functioning; e) Social functioning; f) Mental health; g) Energy-fatigue; h) Health distress; i) Cognitive functioning; j) Quality of life; and k) Health transition. For each dimension and for the survey as a whole a score on the scale of between 0 and 100 is obtained.

All the patients were interviewed by the researchers participating in the ARPAS study, although they were able to self-complete the questionnaires, following the researchers’ instructions. Neither the sponsors nor the main researchers had access to any personal information.

The study was approved in the corresponding ethics committees for clinical research and/or observational studies committees.

A sensitivity analysis was performed based on patient stratification into compliant and non-compliant patients. Similarly, a sensitivity analysis was performed based on the regimen taken by each patient; qd dosing schedule as opposed to other dosing schedules: bid, three or more daily doses (tid).

**Statistical analysis**

For descriptive statistics, mean values have been calculated with their standard error (SE) and standard deviation (SD), as were medians and interquartile range (IQR). The comparison of independent quantitative variables complying with the provisions of the normal law and the homogeneity of variances has been achieved using the Student’s t-test. The contrast of the variables with a normal distribution has been carried out using the Kolmogorov-Smirnov test with the Lilliefors significance level. Given the size of the sample, no non-parametric tests were performed, regardless of the distribution of the variables. The significance test chosen for comparing proportions (association of categorical variables) was the Pearson Chi square test ($\chi^2$). When the frequency of any of the variables was below 5, the comparison was made using the Fisher’s exact test.

A univariate analysis has been performed, stratified in accordance with the compliant/non-compliant classification of the patients obtained with the SMAQ. An analysis of bivariate correlations was carried out to quantify the degree of relationship among the quantitative variables using the Pearson product-moment correlation coefficient. The comparison of the mean values of dependent variables with regard to independent categorical variables has been developed using a one-way analysis of variance (ANOVA), applying the Bonferroni correction factor for multiple comparisons.

The association between compliance and satisfaction and HRQL, estimated with the ESTAR and MOS-HIV questionnaires, respectively, has been studied using a non-conditional logistic regression multivariate analysis, in a manner that the dependent variable was compliance (compliant versus non-compliant patients) and the independent variables were the score obtained from the ESTAR and the MOS-HIV questionnaires, in total and for each of the subscales and dimensions. The control variables were also studied to adjust the association. The logistic regression model is presented for each variable using the odds ratio (OR), its confidence interval at 95% probability (CI95%) and the statistical significance of the association, adjusted for the set of control variables. The significance level was taken to be $\alpha = 0.05$ in all the tests.

**RESULTS**

Thirty two pharmacy departments recruited 234 patients (74% males), with an average age of 43.2 ± 7.8 years, fulfilling the criteria for inclusion. The average time passed since diagnosis of HIV infection and from the initiation of ART until the date of conducting the study was 10.1 ± 5.7 and 7.4 ± 4.4 years respectively. Table I shows the sociodemographic and clinical variables characterising the sample of the patient population in the ARPAS study in accordance with compliance. No significant differences were observed between compliant and non-compliant patients, except in the average time passed since the diagnosis of HIV infection, significantly shorter in compliant patients (9.5 vs. 11.1 years, $p = 0.040$), and in the percentage of patients coinfected with HIV and the hepatitis C (HCV) (35 vs. 48%, $p = 0.042$).

Table II shows the characteristics of the patients’ therapies. The most common therapeutic regime among the patient population was bid, in 71.4% of patients ($n = 167$), followed by qd, administered to 21.4% ($n = 50$). The compliance of 222 patients was evaluated with the SMAQ questionnaire; 47.3% of them were seen to be compliant ($n = 105$). The percentage of patients on qd complying with ART was higher, although not significantly, than patients on bid (55.3% compliant qd, 45.1% compliant bid, $p = 0.251$). Likewise, in patients on qd, a significantly higher compliance was registered with DR in comparison to patients on bid (98 vs. 92%, $p = 0.001$). The average value of DR, considering all the patients, was 95 ± 12%, with an average count time of 7 ± 2.5 months. Applying a cut-off point of 90% to the DR (DR\(_{90}\)), 82% of the patients were classified as compliant, although only 97 patients (44%) were simultaneously compliant in the DR\(_{90}\) and in the SMAQ. With the DR ≥ 95% (DR\(_{95}\)) cut-off point, the percentage of compliant patients was 72%, and 90 patients (41%) were considered
Table I. Sociodemographic and clinical characteristics of patients participating in the ARPAS study, in total and stratified into compliant and non-compliant patients in accordance with the SMAQ questionnaire

<table>
<thead>
<tr>
<th>Sociodemographic variables</th>
<th>Total</th>
<th>Compliant</th>
<th>Non-compliant</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% males)</td>
<td>74%</td>
<td>76%</td>
<td>71%</td>
<td>0.377</td>
</tr>
<tr>
<td>Age (years - SD)</td>
<td>43.2 (7.8)</td>
<td>44.5 (8.8)</td>
<td>42.5 (6.6)</td>
<td>0.062</td>
</tr>
<tr>
<td>Educational level (% with secondary/university qualifications)</td>
<td>49%</td>
<td>50%</td>
<td>47%</td>
<td>0.710</td>
</tr>
<tr>
<td>Employment status (% working patients)</td>
<td>49%</td>
<td>50%</td>
<td>49%</td>
<td>0.849</td>
</tr>
</tbody>
</table>

Clinical variables

| Years since diagnosis HIV+ (SD) | 10.1 (5.7) | 9.5 (6.2) | 11.1 (5.0) | 0.04 |
| CD4 – T-cells/10^3/ml – (SD) | 522.6 (279.5) | 546.0 (281.4) | 511.6 (275.4) | 0.37 |
| % patients CD4 < 200 | 9% | 4% | 12% | 0.029 |
| 200 < CD4 < 350 | 23% | 28% | 17% |
| CD4 > 350 | 68% | 68% | 71% |
| Plasma viral load-HIV RNA copies/ml – (ED) | 3,168 (28,131) | 3,666 (16,576) | 0.88 |

Table II. Characteristics of treatments of the patients participating in the ARPAS study, in total and stratified into compliant and non-compliant patients in accordance with the SMAQ questionnaire

<table>
<thead>
<tr>
<th>Treatment variables</th>
<th>Total</th>
<th>Compliant</th>
<th>Non-compliant</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years since initiation of ART mean value (SD) [median IQR]</td>
<td>7.4 (4.4)</td>
<td>6.9 (4.5)</td>
<td>8.3 (4.2)</td>
<td>0.024</td>
</tr>
<tr>
<td>Different ART since initiation mean value (SD) [median IQR]</td>
<td>3.6 (2.6)</td>
<td>3.3 (2.4)</td>
<td>4.1 (2.7)</td>
<td>0.028</td>
</tr>
<tr>
<td>Different ART during last year mean value (SD) [median IQR]</td>
<td>1.0 (0.8)</td>
<td>0.9 (0.9)</td>
<td>1.1 (0.8)</td>
<td>0.200</td>
</tr>
<tr>
<td>Total number of daily doses mean value (SD) [median IQR]</td>
<td>1.9 (0.5)</td>
<td>1.8 (0.5)</td>
<td>1.9 (0.6)</td>
<td>0.065</td>
</tr>
<tr>
<td>Total pharmaceutical forms/doses mean value (SD) [median IQR]</td>
<td>3.2 (1.7)</td>
<td>3.0 (1.6)</td>
<td>3.4 (1.8)</td>
<td>0.109</td>
</tr>
<tr>
<td>Total no. of daily pharmaceutical forms mean value (SD) [median IQR]</td>
<td>5.9 (3.3)</td>
<td>5.2 (3.0)</td>
<td>6.5 (3.8)</td>
<td>0.006</td>
</tr>
<tr>
<td>% of patients qd</td>
<td>21%</td>
<td>25%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>bid</td>
<td>71%</td>
<td>71%</td>
<td>74%</td>
<td>0.371</td>
</tr>
<tr>
<td>tid</td>
<td>6%</td>
<td>5%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>ND</td>
<td>2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dispensing record mean value % (SD)</td>
<td>95.2 (12.1)</td>
<td>98.0 (10.2)</td>
<td>92.3 (13.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Months of dispensing mean value (SD)</td>
<td>7.0 (2.5)</td>
<td>7.3 (3.2)</td>
<td>6.8 (1.7)</td>
<td>0.180</td>
</tr>
</tbody>
</table>

SD: Standard deviation; IQR: Interquartile range; ND: Not declared.
ART, corresponded to a qd schedule, without evidence of differences with regard to other dosing schedules (Fig. 2).

With regard to their satisfaction with the ART, the scores obtained with the ESTAR were higher in compliant patients in comparison with non-compliant patients. These differences became significant on the satisfaction with lifestyle subscale and the overall ESTAR score, but not with the clinical satisfaction subscale (Table IV). With regard to HRQL, compliant patients showed a higher score in all dimensions, especially significant in the following: health perception, physical functioning, mental health, energy, cognitive functioning, quality of life and on the MOS-HIV total score (Table V). The logistic regression models (Table VI) confirmed the results of the univariate analysis, and a significant association was observed between compliance and the overall satisfaction with ESTAR. Furthermore, a significant association was observed between compliance and the satisfaction subscale related to lifestyles. As regards HRQL, as well as significant association between compliance and the
Table IV. Satisfaction with the ART measured with the ESTAR and stratified according to compliance with the ART

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Mean value % (SD)</th>
<th>n Total</th>
<th>n Compliant</th>
<th>n Non-compliant</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical satisfaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with ART*</td>
<td></td>
<td>218</td>
<td>5.8 (1.2)</td>
<td>104</td>
<td>6.0 (1.1)</td>
</tr>
<tr>
<td>Satisfaction with lifestyle*</td>
<td></td>
<td>218</td>
<td>4.6 (1.5)</td>
<td>104</td>
<td>4.9 (1.4)</td>
</tr>
<tr>
<td>Overall satisfaction with ART*</td>
<td></td>
<td>218</td>
<td>48.5 (8.9)</td>
<td>104</td>
<td>50.4 (7.8)</td>
</tr>
</tbody>
</table>

SD: Standard deviation. *Weighted score according to the factor analysis.

Table V. Descriptive analysis of the dimensions included in the MOS-HIV quality-of-life questionnaire stratified into compliant and non-compliant patients

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Mean value % (SD) [scale 0-100]</th>
<th>n Total</th>
<th>n Compliant</th>
<th>n Non-compliant</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>General health perception</td>
<td>62.0 (20.5)</td>
<td>229</td>
<td>65.9 (19.4)</td>
<td>103</td>
<td>75.7 (20.4)</td>
</tr>
<tr>
<td>Pain</td>
<td>82.3 (21.7)</td>
<td>228</td>
<td>82.9 (22.9)</td>
<td>117</td>
<td>80.9 (21.2)</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>87.6 (14.9)</td>
<td>232</td>
<td>91.5 (13.3)</td>
<td>117</td>
<td>85.7 (15.1)</td>
</tr>
<tr>
<td>Role functioning</td>
<td>89.5 (17.9)</td>
<td>233</td>
<td>91.6 (15.8)</td>
<td>117</td>
<td>87.0 (19.6)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>91.2 (16.5)</td>
<td>230</td>
<td>91.3 (15.7)</td>
<td>116</td>
<td>90.9 (16.4)</td>
</tr>
<tr>
<td>Mental health</td>
<td>73.7 (17.2)</td>
<td>229</td>
<td>78.4 (16.2)</td>
<td>103</td>
<td>69.0 (16.9)</td>
</tr>
<tr>
<td>Energy</td>
<td>71.1 (19.0)</td>
<td>229</td>
<td>74.8 (19.6)</td>
<td>114</td>
<td>66.7 (17.9)</td>
</tr>
<tr>
<td>Health distress</td>
<td>85.2 (17.3)</td>
<td>227</td>
<td>87.1 (16.9)</td>
<td>115</td>
<td>82.9 (18.0)</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>82.9 (16.3)</td>
<td>232</td>
<td>86.1 (14.9)</td>
<td>117</td>
<td>79.1 (17.1)</td>
</tr>
<tr>
<td>Quality of life</td>
<td>70.5 (15.8)</td>
<td>232</td>
<td>73.0 (14.5)</td>
<td>117</td>
<td>67.5 (16.1)</td>
</tr>
<tr>
<td>Health transition</td>
<td>66.8 (14.8)</td>
<td>232</td>
<td>68.5 (14.7)</td>
<td>117</td>
<td>65.3 (14.9)</td>
</tr>
<tr>
<td>MOS overall score</td>
<td>78.7 (11.7)</td>
<td>212</td>
<td>81.6 (10.7)</td>
<td>108</td>
<td>75.7 (11.3)</td>
</tr>
</tbody>
</table>

SD: Standard deviation.

Table VI. Degree of association of satisfaction and quality of life with compliance according to the logistic regression models

<table>
<thead>
<tr>
<th>Predictor variables</th>
<th>OR</th>
<th>CI95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subscales of satisfaction with</td>
<td>1.279</td>
<td>1.037-1.577</td>
<td>0.021</td>
</tr>
<tr>
<td>lifestyle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical satisfaction subscale</td>
<td>1.207</td>
<td>0.945-1.542</td>
<td>0.131</td>
</tr>
<tr>
<td>Overall satisfaction with ART</td>
<td>1.049</td>
<td>1.013-1.086</td>
<td>0.007</td>
</tr>
<tr>
<td>(overall ESTAR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General health perception</td>
<td>1.019</td>
<td>1.005-1.034</td>
<td>0.009</td>
</tr>
<tr>
<td>Pain</td>
<td>1.001</td>
<td>0.988-1.014</td>
<td>0.854</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>1.020</td>
<td>1.000-1.041</td>
<td>0.056</td>
</tr>
<tr>
<td>Role functioning</td>
<td>1.017</td>
<td>1.001-1.033</td>
<td>0.042</td>
</tr>
<tr>
<td>Social functioning</td>
<td>1.001</td>
<td>0.984-1.019</td>
<td>0.903</td>
</tr>
<tr>
<td>Mental health</td>
<td>1.034</td>
<td>1.015-1.054</td>
<td>0.000</td>
</tr>
<tr>
<td>Energy</td>
<td>1.023</td>
<td>1.007-1.039</td>
<td>0.005</td>
</tr>
<tr>
<td>Health distress</td>
<td>1.012</td>
<td>0.995-1.029</td>
<td>0.159</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>1.028</td>
<td>1.009-1.048</td>
<td>0.004</td>
</tr>
<tr>
<td>Quality of life</td>
<td>1.022</td>
<td>1.003-1.042</td>
<td>0.024</td>
</tr>
<tr>
<td>Health transition</td>
<td>1.012</td>
<td>0.992-1.032</td>
<td>0.243</td>
</tr>
<tr>
<td>Overall MOS-HIV</td>
<td>1.045</td>
<td>1.017-1.075</td>
<td>0.002</td>
</tr>
</tbody>
</table>

OR: Odds ratio; CI95%. Confidence interval of 95%.

MOS-HIV overall score, significant associations were observed between compliance and the dimensions of general health perception, role functioning, mental health, energy, cognitive functioning and quality of life. The control variables used to adjust the association were selected according to the results of the univariate analysis, so that the logistic regression models were adjusted by gender, age, therapeutic regimen and HCV coinfection. The choice of these control variables is supported by numerous studies which have shown the relationship between these and compliance.

DISCUSSION

The study design, limited to 230 patients because of the resources available for carrying it out, justifies the competitive multicentre recruitment, which ensured the patient profile was representative of the HIV+ patient receiving ART in Spain; aged over 40 years, 74% male, mostly with bid dosing schedule, HIV-HCV coinfection in more than 40% of the patients and an average CD4 lymphocyte value of around 500 cells/ml.

It seems evident that simplifying the dosing regimen, the number of pharmaceutical forms or the number of daily doses, is a factor favouring compliance, although this relationship has not been completely shown given that, on the one hand, most studies are not specifically designed to show this relationship and, on the other, many of the studies were conducted during periods when highly active antiretroviral therapy (HAART) used to comprise a large number of pharmaceutical forms, daily doses and was accompanied by numerous and frequent adverse effects. Furthermore, there is not sufficient consistency to relate compliance with sociodemographic characteristics, quality of life, knowledge and beliefs of the patients or satisfaction with the healthcare received.

At present, the most frequently-used HAART schedules comprise a low number of pharmaceutical forms and are mostly administered in one or two daily doses. As a result, the relative importance of these variables on compliance has substantially changed, as can be seen in the results of the ARPAS study, in which it can be observed that the time since diagnosis with HIV infection and from the initiation of ART, as well as the number of previous ART, are different depending on the patient compliance, but they are not substantially affected by the number of doses, although it has been seen that compliant patients take a smaller number of pharmaceutical forms every day than those who are not compliant.

The percentage of compliant patients in the ARPAS study, estimated with the SMAQ questionnaire, is considerably lower (47.3%) than in the original study validating this questionnaire (62.5%). This discrepancy could be due to the moments when each of the studies were conducted; the GEEMA study was conducted...
between January 1998 and December 1999, years during which the antiretroviral combinations were less powerful, making great demands on the patients for compliance, and were worse tolerated in comparison with current treatment regimens. Although these characteristics could be related to poorer compliance or adherence, it must be remembered that the HAART and the relationship between therapeutic failure and lack of compliance with it were very new concepts (HAART were introduced into clinical practice in 1996), meaning that the involvement of the patients, who were still very close to the time when mortality rates were high, and of healthcare professionals with compliance with ART was greater then than it is now, being this one of the main factors insisted on in order to achieve success in the treatment. As a result, although in that period the characteristics of the ART did not encourage compliance, it is feasible that this was greater than it is now. However, in more recent publications, some authors refer, as we found in our study, to a low percentage of compliant patients, 47% estimating compliance by questionnaire and 53% estimating compliance as missed doses in the three days prior to the interview. One aspect that could influence on the low percentage of compliant patients obtained in the ARPAS study is the fact that the patients filled in the SMAQ in the pharmacy departments and not at medical consultations, in a manner which patients could feel less “pressure” and, therefore, did not overvalue their behaviour in relation to their taking of ART. Furthermore, the compliance estimated by quantitative measures, in our case with the DR, showed a clear overestimation and lack of similarity to the results of the SMAQ. This effect has already been seen in other studies, which obtain patient compliance percentages over 85% 6-35,36. This important discrepancy between the methods used highlights the need to continue to research tools that allow compliance estimation to be optimised 39,40.

Compliance is a dynamic concept, meaning that a cross-sectional study is not sensitive enough to detect changes. The finding that the longer the time of evolution of the infection and from the initiation of ART, the percentage of compliant patients is lower, leads us to think that compliance worsens over time, although there is not enough evidence to confirm this observation. This finding was also observed by Reynolds et al. 39, who found a relationship between positive beliefs or those encouraging compliance and cognitive, emotional and social functioning, the lower age and the higher level of education. Another limitation of the cross-sectional design is the impossibility of assigning causality to the fact that we find a greater percentage of compliant patients among those taking their ART in a qd regimen or those taking the smallest number of pharmaceutical forms every day. As a result, it is not possible to confirm that the decreased daily number of doses or pharmaceutical forms is a “facilitating” factor for compliance. It can only be concluded that, in our sample, the patients classified as compliant using the SMAQ were taking ART regimes with a smaller number of daily pharmaceutical forms. Checking this association would require a multivariate analysis and a longitudinal design, which allowed an analysis of sensitivity to change to be made; i.e., to what extent compliance changes after the number of doses or number of daily pharmaceutical forms are changed.

No differences were found in the clinical variables in this study with regard to the patients being compliant or not compliant. A longitudinal study, with sufficient time and patients, would probably show, at the end, a greater number of therapeutic failures, higher plasma viral load and lower CD4 T-lymphocyte count in non-compliant patients.

The self-evaluation of the patients taking the medication was good, and they considered the medication easy to take. However, there is an elective preference for the qd regimen. Most patients on qd treatment (92%) said it was easy to take their medicine, against 78.9% on the bid regimen and 70.6% on tid. The preference for the qd regimen was evident from the answers to the other questions. However, with regard to the characteristics of the ART, effectiveness, durability and tolerance are considered the most important attributes by the patients, over and above convenience of administration. As a result, it can be concluded that two independent levels must be considered with regard to the TAR; on the one hand, the characteristics of each of the medications, in which case patients sacrifice convenience for effectiveness and, on the other, the elective preferences between two or more different treatment regimens, which are assumed to have similar effectiveness.

This same tendency has already been shown in other studies; in the Scherer et al. study, 92% of patients prefer a more effective bid regimen to a qd, while 89% prefer a more durable bid treatment 41. In another European study with 504 patients 41, they consider that qd treatment is the one that best adapts to their lifestyle and, together with the reduction in the number of pharmaceutical forms, it could contribute to improving compliance. However, both power and side effects are the most important characteristics for choosing an ART. Similarly, in the Miller et al. study 42, patients preferred to sacrifice the characteristics that influence their quality of life for the sake of a more powerful regimen. However, in the same way that in the ARPAS study, when comparing similar power ART’s, the patients stated the importance of a small number of doses and pharmaceutical forms 43.

With regard to safety, the most difficult event to overcome is lipoatrophy/lipodystrophy (question about changes in their physical figure). The side effects relating to the gastrointestinal tract (10.6% for diarrhoea and 10.6% for gastrointestinal disorders) lag considerably behind. However, in former studies, such as that by Bertholon et al. 44, the most commonly cited adverse effects were fatigue and gastrointestinal problems. In a
more recent study by Scherer et al., patients point out, as the most important side effects, those affecting their physical appearance. This change in patient preferences and concerns, associated with the evolution of the infection and the ART, shows the importance and need to incorporate their preferences to the outcome variables regularly measured in general clinical practice. Finally, the low use of pharmacists as a source of information, already observed by Bertholon et al. in 1999, forces us to suggest new care strategies from the hospital pharmacy departments, even more so when these play an increasingly active role in pharmaceutical monitoring of HIV+ patients.

As well as the relationship of the clinical and therapeutic variables to compliance, the least studied aspect is that of the relationship between compliance and satisfaction.

This is probably due to the very few studies regarding satisfaction with ART and the difficulties involved in measuring it because of a lack of validated methods. There are few works studying the relationship between compliance and satisfaction with ART. A direct relationship has been observed between compliance and what could be called satisfaction with the healthcare received, this being taken as the relationship between the patient and healthcare professionals. In the ARPAS study, the direct relationship between compliance and satisfaction with ART is confirmed both in the univariate and multivariate analyses, as all the questions in the ESTAR questionnaire show a higher, significant score for compliant patients in comparison with non-compliers. However, the main limitation lies in its cross-sectional design, which does not enable the evolution of satisfaction and compliance to be known in the long term. In the same sense as satisfaction, most of the dimensions contemplated in the MOS-HIV questionnaire have shown significantly higher scores in compliant patients. Other studies have confirmed this association between compliance and health perception, the functional condition and the social, emotional and cognitive functioning.

To conclude, the ARPAS study, carried out by specialist pharmacists in hospital pharmacy departments and including 234 HIV+ patients, describes the preferences of patients on ART, as well as compliance, satisfaction and quality of life. With regard to preferences, our study concludes that the HIV+ patients place more value on the treatment efficacy than on other characteristics such as tolerance and convenience (number of pharmaceutical forms and doses). Most patients find it easy to take their medication, but if given the option, they prefer the qd regimen. With regard to the adverse effects, it is worth pointing out the importance patients give to changes in their figure. Knowledge of patient preferences can be helpful when it comes to choosing ART, but tools are needed to allow the evaluation of these preferences to be updated according to changes in the ART. The outcomes of the ARPAS study show the clear relationship between compliance and satisfaction with ART and between compliance and HRQL, meaning that the improvement strategies for compliance shall necessarily include aspects that allow patient satisfaction with the ART they take and their quality of life to be improved in general terms and, in particular, in dimensions such as health perception, mental health, energy and cognitive functioning.

Alphabetical list of the 93 researchers participating in the ARPAS study

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Appendix I. Questionnaire on treatment regimen and preferences of HIV+ patients

1. Please, score from 1 (I take it very badly, I don’t take it) and 10 (I never miss a dose and I take my tablets at the right times and with or without food, according to the recommendations I have been given) how do you think you are taking your medication (with regard to compliance, timetables, omissions, etc.)

2. How difficult is it for you to take your medication at the times you have been recommended? (e.g., taking the medication at the same times every day, with an interval of ± 1 hour)

   - Very difficult
   - Difficult
   - Somewhat difficult
   - Easy
   - Do not know/no answer

3. Which of the following options do you prefer?

   - Taking tablets in the morning and at night
   - Taking tablets at night
   - Taking tablets in the morning, at midday and at night
   - I am not bothered
   - Do not know/no answer

4. On a scale of 1 (no interest) to 10 (very interested), how would you score the once-daily treatment?

5. State which regimen you would find easiest to comply with:

   - (Tick one box for each question)

<table>
<thead>
<tr>
<th>Once a day (every 24 h)</th>
<th>Twice a day (every 12 h)</th>
<th>Three times a day (every 8 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. I tend to get distracted and sometimes, I miss some of the doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. My daily routine changes frequently</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. The convenience of carrying the medicines on me and being able to take them outside the home</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. I want to “forget” that I am ill and do not want the treatment to remind me of it</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e. Privacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>f. I would take the tablets better</td>
<td></td>
<td></td>
</tr>
<tr>
<td>g. Stress remembering how to take the tablets</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6. If your CD4 levels and viral load are good, would you change your current medication for one that was easier to take?

   - No, I would not change it
   - Yes, in any event
   - Yes, but only if it meant taking it once a day
   - Yes, but only if it meant taking fewer tablets every day
   - Do not know/no answer

7. Rank, in order of importance (1 is the most important, 2 is the second most important and so on and so forth) each of the following characteristics of antiretroviral medicines:

   - Power
   - Futures options and less resistance
   - Adverse effects
   - Convenience of taking the treatment (no. of tablets and no. of doses)
### Appendix I. Questionnaire on treatment regimen and preferences of HIV+ patients (continued)

8. What reasons would you have for stopping, no longer taking the treatment or delaying its start? Rank the options in order of importance (1 the most important, 2 is the next most important, and so on)

<table>
<thead>
<tr>
<th>Reason</th>
<th>Order</th>
</tr>
</thead>
<tbody>
<tr>
<td>Too many tablets</td>
<td></td>
</tr>
<tr>
<td>A lot of daily doses</td>
<td></td>
</tr>
<tr>
<td>Adverse effects</td>
<td></td>
</tr>
<tr>
<td>Preserve options for future treatments</td>
<td></td>
</tr>
<tr>
<td>If the infection is well controlled, stop taking the treatment for a while (pharmacological break)</td>
<td></td>
</tr>
<tr>
<td>The treatment is not effective</td>
<td></td>
</tr>
</tbody>
</table>

9. There is a great variety of adverse events produced by taking medications for HIV infection. I am going to read you a list of adverse events. Could you tell me which the most difficult adverse event to endure is? I am not asking you whether you suffer from any of these side effects, but which you think would be the most difficult to endure.

- High cholesterol
- Changes to my figure
- Trembling hands, legs and feet
- Fatigue
- Diarrhoea
- Stomach disorders or nausea
- Headache
- Rash
- Hypersensitivity (allergy to any medicines)
- Do not know/no answer

10. Indicate which source of information you find the most useful. Answer with a maximum of three, and rank them (with numbers) in importance:

- Internet
- Friends/acquaintances/relatives/patient associations
- Pharmacist
- Doctor in medicine
- Nurse
- Psychologist
- Media
- Pharmaceutical companies
- Journals on HIV
- Governmental publications
- Do not know/no answer

THANK YOU FOR YOUR COLLABORATION

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CONFLICT OF INTERESTS
Gilead Sciences SL has collaborated with the Spanish Hospital Pharmacy Foundation by sponsoring the ARPAS study, without intervening in any aspects regarding the design, promotion, monitoring or analysis and outcome assessment. Furthermore, the authors of this manuscript declare their total independence regarding the outcome assessment and they do not represent any organisations or groups.

References


Preferences, satisfaction and compliance with antiretroviral treatment: ARPAS study (II)

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