Influence of the number of daily pills and doses on adherence to antiretroviral treatment: a 7-year study

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SUMMARY

What is known and objective: **Antiretroviral treatment (ART) is hampered by complicated regimens, high pill burden, drug–drug interactions, and frequent short- and long-term adverse effects, leading to decreased adherence. Over recent years, considerable effort has been directed at developing regimens that are less burdening. We undertook a 7-year retrospective study of the records of 264 HIV-infected subjects enrolled in a pharmaceutical care programme to document the progress made and to study the influence of the number of ART pills and doses on the level of treatment adherence.**
Methods: **Antiretroviral dispensing records were analysed for the number of pills and doses administered and the ART adherence rate estimated.**
Results and discussion: **In 2005, the patients took a mean of 6·2 pills daily (CI 95%: 5·9–6·6), and 92·9% of them were on a twice-a-day (BID) dosage regimen. By 2012, the mean number of pills was reduced to 4·1 (CI 95%: 3·8–4·4), and only 50·9% were on a BID regimen. No statistically significant relation was observed between number of daily pills and doses and ART adherence reached by the patients in any of the analyses performed.**
What is new and conclusions: **There has been a continuous reduction in the number of pills and doses of antiretrovirals taken by individual patients over the last 7 years due largely to the introduction of improved treatments and regimens. More daily pills or doses was not associated with worse ART adherence in our pharmaceutical care programme.**

WHAT IS KNOWN AND OBJECTIVE

Antiretroviral treatment (ART) aims to improve survival and quality of life of the patients with HIV infection and reduce transmission of the infection. These are achieved by maintaining the CD[4+] lymphocytes count within the normal range and obtaining complete control of viral replication.[1]

ART has been steadily improving particularly since the introduction of potent combination therapy in 1996. New drugs with new mechanisms of action, improved potency and activity even against multidrug-resistant viruses, dosing convenience, and tolerability have been approved. These newer drugs have dramatically reduced HIV-associated morbidity and mortality and have transformed HIV infection from a rapidly lethal condition into a chronic one.[1] However, the success of ART has been hampered by complicated regimens, high pill burden, drug–drug interactions, and frequent short- and long-term adverse effects, leading to decreased adherence to prescribed regimens. Currently, lack of adherence to ART continues to be one of the principal factors in therapeutic failure and the development of viral resistance.[2,3]

Adherence is the result of a complex process that involves acceptance of the diagnosis, perception of the need to correctly carry out the treatment, and motivation to do so. Furthermore, possession of appropriate skills, ability to overcome any difficulties that appear and maintenance of the level of achievement reached over time are necessary.[4] The development of strategies for improving ART adherence requires knowledge of the influential factors and how these factors exert their effects. In general, it is accepted that motivational and daily-habit-modifying strategies are the most effective ones.[5–7]

Several studies have shown that the characteristics of the antiretroviral regimens may affect ART adherence. These studies have described a direct association between antiretroviral treatment non-adherence and burden in the number of pills.[8,9] Higher adherence levels have been reported in patients on a once-daily (OD) vs. twice-daily (BID) or three-times-a-day (TID) regimens.[10–13] Due to these findings, a concerted effort has been made to reduce both pill burden and dosing frequency.[14,15] Two types of improvements are possible. The first is based on optimizing the presentation of each medication by increasing the amount of drug contained in each pill or increasing its half life. The second involved including two or more antiretrovirals into one pill.

This study aimed to analyse the evolution over time of the number of ART pills and doses taken by individual patients and the influence of these factors on the level of treatment adherence by a group of HIV-infected patients participating in a pharmaceutical care programme.

METHODS

A 7-year long retrospective study with data from HIV-infected patients treated in the Pharmacy Service outpatient unit of the

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University Hospital of Salamanca, Spain was conducted (April 2005–April 2012). Inclusion criteria were as follows: patients with confirmed HIV infection who had been receiving ART in our hospital during the entire study period.

Adherence measures

Many scientific studies and consensus documents have recommended the use and combination of at least two adherence evaluation methods to yield reliable results.[1,16] Therapeutic drug monitoring (TDM) (direct method), antiretrovirals dispensing records (DR) and simplified medication adherence questionnaire (SMAQ)[17] (indirect methods) are routinely used in our care practice.

A previous 5-year study of ours showed a correlation between DR and SMAQ (measurement of self-reported adherence by the patient) during the study period.[18] The current study used the DR method because it makes possible the quantification of adherence as a continuous variable. Adherence was calculated, for 6-month periods beginning from the initiation of the study (April 2005). The adherence level for each period was obtained from the number of pills taken during that period divided by the number of pills prescribed during the same period. Levels that exceeded 100% were rounded down to 100%. Patients who consumed ≥95% of the medication prescribed were considered 'adherent patients'.[19]

Daily pills and doses

Antiviral treatment was characterized by the number of pills and doses that the patient needed per day. This number was obtained from the DR for each patient using 6-month periods beginning at the onset of the study. This was compared with adherence in these same periods. For patients who had switched treatment, the number of pills and doses corresponding to the longest period within the 6-month period evaluated was used.

The analysis strategies were based on the study of the following relationships:
1 Relationship between the number of daily pills or doses with the level of adherence. Adherence was used as a continuous variable and categorized into two levels: ≥95% vs. <95%.
2 Relationship between the change in the number of daily pills or doses with the change in adherence level.
3 Relationship between the number of daily pills or doses with adherence level stratified into four categories at the start and end of the study (<60%, 60–79%, 80–94%, 95–100%).[19] The percentage of patients in the total population with the same number of pills or doses was calculated in each case. The cut-off for number of pills corresponds to the number that optimized sampling sizes: four and three for the baseline and final situation, respectively. Cut-off for dose number was one.

Statistical analyses

The chi-square test for independence, also called Pearson's chi-square test, was used to study if there was a relationship between categorical variables. Spearman's correlation was used to study the relationship between quantitative or ordinal variables and Bonferroni correction was conducted. The Z test was used for the comparison of proportions. Furthermore, logistic regression models were constructed to investigate the association of the number of pills or doses with the dichotomous outcomes of adherence (<95%

vs. ≥95%). IBM SPSS Statistics for Windows version 20.0.0.2[20] and Epidat 3.1[21] were used for the statistical analyses.

RESULTS

A total of 264 patients who received pharmacological treatment during the entire study period were included. Baseline demographic and clinical characteristics of the total study population are given in Table 1.

Evolution of the number of daily pills and doses during the study

During the 7 years of the study, 3610 records of the number of pills and the same number of records for doses in the patients enrolled were obtained. Evolution of the number of daily pills or doses during the study is shown in Fig. 1(a) and Table S1.

In addition, the evolution in the number of pills at the beginning and end of the study based on whether treatment was administered in a OD, BID or TID regimen was studied. The results are shown in Table 2.

The evolution in time of the percentage of the patients who were using the less complex regimens, that is less than five antiretroviral pills per day and/or a single dose per day, was also analysed [Fig. 1(b)].

Relation between pills and doses with adherence

Three different strategies were used to analyse the possible relation between the number of pills or doses and adherence:

Relation between the number of daily pills or doses with adherence in each studied period. No significant relation was observed when adherence was studied as a continuous variable. However, all the estimated correlations have the expected sign ($\hat{\rho} < 0$), indicating a decrease of adherence when the number of daily pills or doses increases.

On the other hand, when adherence was categorized into two levels, no clear pattern was found in the logistic regression analysis to relate number of daily pills and doses with adherence or non-adherence.

Relation between the change in number of daily pills and doses with the change in adherence in each studied period. No statistically significant relation was found between the change in number of pills and

Table 1. Baseline demographic and clinical characteristics of study population

Characteristics	Values Mean ± SD (range) or *n* (%)
Age (years)	40·58 ± 8·81
Male	180 (68·2)
Number of years on ART	5·35 ± 3·60
CD$_{4+}$ counts (cells/mcL)[a]	398·16 ± 240·57
Undetectable plasma viral load[a]	191 (85·3)

SD, standard deviation; *n*, number; ART, antiretroviral treatment.
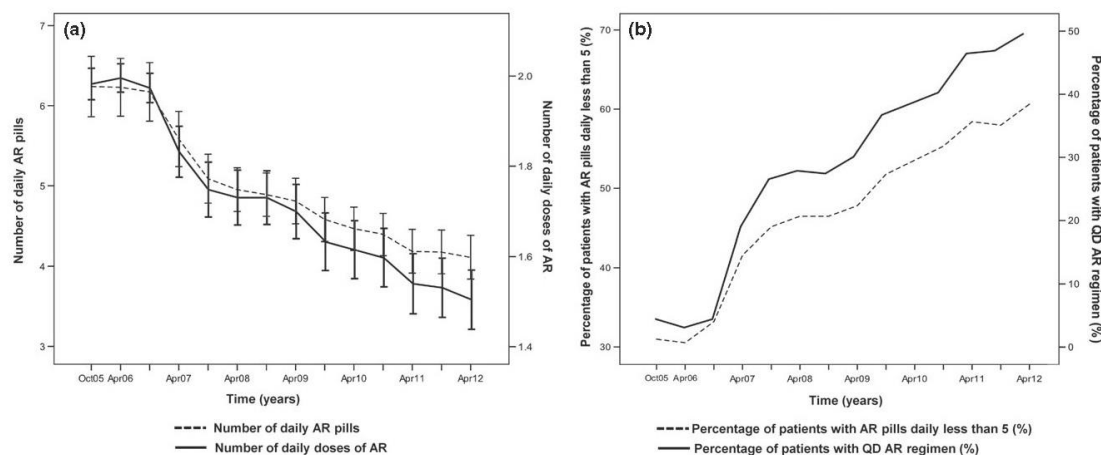[a]The variable only refers to those patients for whom these clinical data were available.

Fig. 1. Mean number of daily pills and doses during the study period (a) and percentage of patients taking less than five pills daily and that of patients on the OD regimen (b). AR, antiretrovirals; OD, once a day.

Table 2. Number of patients and number of daily pills at the beginning and end of the study, based on type of administration regimen (OD, BID or TID)

	Administration regimen					
	OD		BID		TID	
	Baseline	Final	Baseline	Final	Baseline	Final
Number of patients	10	129	221	134	7	0
Number of daily pills Mean (range)	3·5 (2–5)	2·8 (1–6)	6·2 (2–15)	5·4 (2–10)	8·1 (4–12)	–

OD, once a day; BID, twice a day; TID, three times a day.

doses in each patient with the change in adherence in the period studied or in the period immediately follow it.

Relation between number of daily pills and doses with adherence stratified into four categories at the onset and end of the study. Regarding number of pills, 157 patients showed high pill burden at the beginning of the study (>4 pills) and 140 patients at the end of it (>3 pills). It can be observed that: (i) the percentage of adherent patients was greater than the non-adherent, both globally and by the number of pills; (ii) the percentage of patients with optimal adherences was slightly greater in the patients who took fewer pills; and (iii) there were no statistically significant differences between the two groups in any of the four adherence sections (Fig. 2).

No statistically significant differences were observed between both groups in any of the four adherence sections in relation to dose (Fig. 3).

The results of analysis at the end of the study established that: (i) there was no patient group in which adherence was less than 60%, (ii) the percentage of patients in the ≥95% adherence range

increased considerably ($P = 0·0015$), and (iii) number of daily pills or doses did not affect adherence reached by the patients.

DISCUSSION

Adequate antiretroviral treatment adherence is undoubtedly one of the fundamental requirements for success.[19,22] For this reason, the study of the different factors that may improve patient adherence with the pharmacotherapy has led to great interest within the scientific and health care setting.[23,24]

The patients included in the study had a mean antiretroviral treatment time (at the onset of the study) of approximately 5 years. Globally, the clinical status of the patients was good, with an approximate mean CD^{4+} lymphocyte count of 400 and undetectable plasma viral load in 85% of the cases.

Evolution of the number of daily pills and doses during the study

The study was initiated in 2005. As can be seen in Table 2, at that time, the patients were taking a mean of 6·2 pills daily, 92·9% of
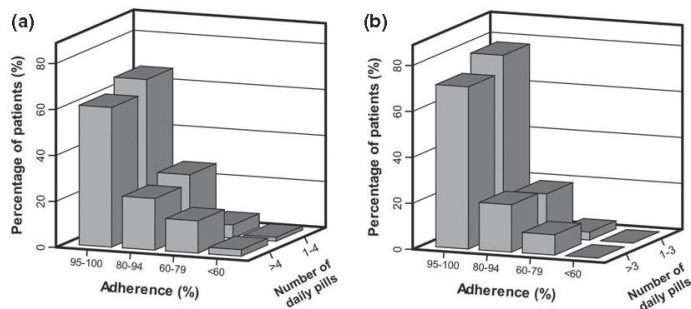
Fig. 2. Percentage of patients, at each adherence level, based on number of daily pills, at the beginning (a) and end of the study (b). Note: patients for whom baseline and final data of number of daily pills and adherence were available ($n = 229$ and $n = 246$, respectively).
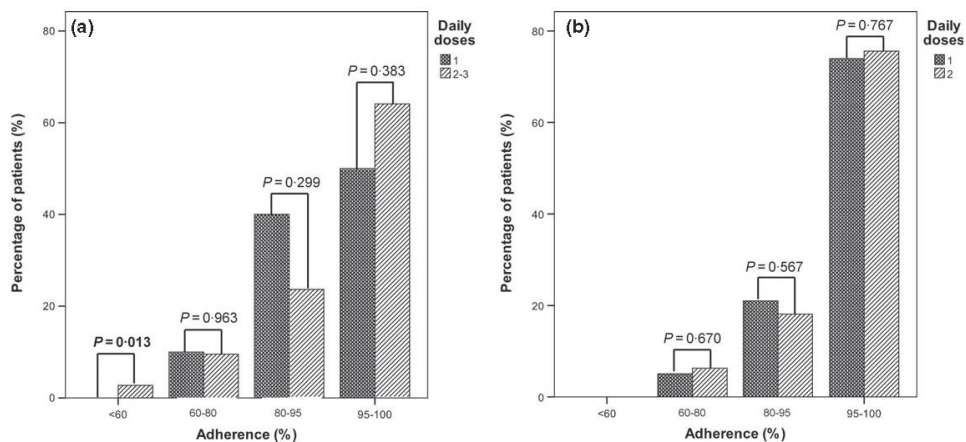

Fig. 3. Percentage of patients, at each adherence level, based on number of daily doses, at the beginning (a) and end of the study (b). Note: patients for whom baseline and final data of number of daily doses and adherence were available ($n = 230$ and $n = 246$, respectively).

them with a BID regimen. At the end of the study (2012), mean number of pills that the patients were taking decreased to 4·1 [Fig. 1(a)] and only 50·9% of them with a BID regimen. The reduction observed in the frequency of use of BID regimens was associated to a considerable increase in the OD regimens. This latter increased from 4·1% in the year 2005 to 49·1% in 2012. The tendency observed in the reduction of the number of doses was been observed in the TID regimens too. These went from 2·9% at the onset of the study to disappearing at the end of it. As can be seen in Fig. 1(b), it should also be stressed that only 32·0% of the patients in 2005 were taking less than five pills and that this amount practically doubled by the end of the study (60·4%).

The spectacular increase of simpler regimens in our population in the period studied can be explained by the marketing of new formulations, by the low frequency of drug resistance mutations in our patient population, and a high proportion of patients on their first treatments. People with first-line regimens are more likely to receive a reduced number of pills and doses. This may in turn have accounted for the high rates of adherence recorded in our population, even at baseline measurement and the prolonged efficacy of treatment.

Consensus does exist that patients prefer the simpler regimens, ideally OD, and those with only one pill.[25–28]

However, no consensus has been found on whether this reduction in the number of pills and doses objectively leads to improvement in patient adherence with their antiretroviral medication.[11,12,29]

Relation between daily pills and doses with adherence

Based on the existing controversy in the literature on the influence of the number of pills and doses on adherence to ART, we carried out this study over a 7-year period. Bearing in mind that the results obtained often depended on the type of analysis performed, on the criteria used and even on the statistical analyses chosen, we considered that it was necessary to analyse the possible influence from different points of view in order to obtain general conclusions that attempt to clarify the information existing up to date:

When the relation between number of pills or doses with adherence was studied, no statistical significance was observed in any of the periods studied. When the changes in the number of pills or doses were compared with changes in adherence, no statistically significant relation between them was observed.

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Finally, no relation was observed between number of pills or doses and whether the patient was ART adherent or non-adherent.

For the number of pills, it appears that the number of times the patient takes the pills per day is more important than the number of pills as more frequent dosing may interfere with the patient's daily activities. Our results on number of pills and doses are similar to those reported in a recent meta-analysis.[30]

Finally, we would like to think that the good results observed reflect positively on the continuous 7-year pharmaceutical care programme. Thus, the patients were instructed on the importance of taking their antiretroviral medication correctly and about not forgetting to take it. In this sense, it is possible that these results cannot be extrapolated to care centres in which this type of follow-up does not exist or to settings in which the antiretroviral drugs are not dispensed centrally in hospital pharmacies. However, our study design does not allow the impact of our programme to be independently estimated.

Many factors influence ART adherence, including demographic factors, clinical management and drug adverse effects and again these could not be assessed independently in our study.

Currently, due to important and growing economic restrictions on health care costs, there is a tendency to 'break up' fixed-dose combinations of antiretrovirals[31] to enable the use of antiretroviral drugs individually, especially with less expensive generic drugs.[32] The savings can be considerable. Our study results suggest that this strategy is unlikely to affect patient adherence, at least in our setting.

WHAT IS NEW AND CONCLUSION

The number of daily pills during the 7-year study period decreased from about six to four. An increase was observed in the frequency of OD regimens instead of BID regimens. No relationship was found between number of daily pills or doses of the antiretroviral medication and adherence in our pharmaceutical care programme.

ACKNOWLEDGEMENTS

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 Evolution of the number of daily pills or doses during the study.

REFERENCES

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Washington, DC: Department of Health and Human Services [updated February 12, 2013]. Available at: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf (accessed 12 April 2013).
2. Murphy P, Cocohoba J, Tang A, Pietrandoni G, Hou J, Guglielmo BJ. Impact of HIV-specialized pharmacies on adherence and persistence with antiretroviral therapy. *AIDS Patient Care STDs*, 2012;**26**:526–531.
3. Tran BX, Nguyen LT, Nguyen NH, Hoang QV, Hwang J. Determinants of antiretroviral treatment adherence among HIV/AIDS patients: a multisite study. *Glob Health Action*, 2013;**6**:19570.
4. Panel de expertos de Secretaría del Plan Nacional sobre el Sida (SPNS); Sociedad Española de Farmacia Hospitalaria (SEFH); Grupo de Estudio del Sida (GESIDA). Mejorar la adherencia al tratamiento antirretroviral. Recomendaciones de la SPNS/SEFH/GESIDA [Improving adhesion to antiretroviral treatment]. *Farm Hosp* 2008;**32**:349–357.
5. Adamian MS, Golin CE, Shain LS, DeVellis B. Brief motivational interviewing to improve adherence to antiretroviral therapy: development and qualitative pilot assessment of an intervention. *AIDS Patient Care STDs*, 2004;**18**:229–238.
6. Ma A, Chen DM, Chau FM, Saberi P. Improving adherence and clinical outcomes through an HIV pharmacist's interventions. *AIDS Care*, 2010;**22**:1189–1194.
7. Holstad MM, DiIorio C, Kelley ME, Resnicow K, Sharma S. Group motivational interviewing to promote adherence to antiretroviral medications and risk reduction behaviors in HIV infected women. *AIDS Behav*, 2011;**15**:885–896.
8. Atkinson MJ, Petrozzino JJ. An evidence-based review of treatment-related determinants of patients' nonadherence to HIV medications. *AIDS Patient Care STDs*, 2009;**23**:903–914.
9. Airoldi M, Zaccarelli M, Bisi L *et al*. One-pill once-a-day HAART: a simplification strategy that improves adherence and quality of life of HIV-infected subjects. *Patient Prefer Adherence*, 2010;**4**:115–125.
10. Maitland D, Jackson A, Osorio J *et al*. Switching from twice-daily abacavir and lamivudine to the once-daily fixed-dose combination tablet of abacavir and lamivudine improves patient adherence and satisfaction with therapy. *HIV Med*, 2008;**9**:667–672.
11. Parienti J, Bangsberg DR, Verdon R, Gardner EM. Better adherence with once-daily antiretroviral regimens: a meta-analysis. *Clin Infect Dis*, 2009;**48**:484–488.
12. Bangsberg DR, Ragland K, Monk A, Deeks SG. A single tablet regimen is associated with higher adherence and viral suppression than multiple tablet regimens in HIV+ homeless and marginally housed people. *AIDS*, 2010;**24**:2835–2840.
13. Assawasuwannakit P, Braund R, Duffull SB. A model-based meta-analysis of the influence of factors that impact adherence to medications. *J Clin Pharm Ther*, 2015;**40**:24–31.
14. Juday T, Correll T, Anene A, Broder MS, Ortendahl J, Bentley T. Cost-effectiveness of the once-daily efavirenz/emtricitabine/tenofovir tablet compared with the once-daily elvitegravir/cobicistat/emtricitabine/tenofovir tablet as first-line antiretroviral therapy in HIV-infected adults in the US. *Clinicoecon Outcomes Res*, 2013;**5**:437–445.
15. Permpalung N, Putcharoen O, Avihingsanon A, Ruxrungtham K. Treatment of HIV infection with once-daily regimens. *Expert Opin Pharmacother*, 2012;**13**:2301–2317.
16. Panel de expertos de GESIDA y Plan Nacional sobre el Sida. National consensus document by GESIDA/National Aids Plan on antiretroviral treatment in adults infected by the human immunodeficiency virus [January 2011 update]. *Enferm Infecc Microbiol Clin* 2011;**29**:209.e1–209.e103.

17. 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**:605–613.

18. Hernández Arroyo MJ, Cabrera Figueroa SE, Sepúlveda Correa R *et al*. Impact of a pharmaceutical care program on clinical evolution and antiretroviral treatment adherence: a 5-year study. *Patient Prefer Adherence*, 2013;**7**:729–739.

19. 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.

20. IBM Corp. *IBM SPSS statistics for windows, version 21.0*. Armonk, NY: IBM Corp., 2012.

21. Hervada Vidal X, Santiago Pérez M, Vázquez Fernández E, Castillo Salgado C, Loyola Elizondo E, Silva Ayçaguer L. Epidat 3.0 programa para análisis epidemiológico de datos tabulados. *Rev Esp Salud Pública*, 2004;**78**:277–280.

22. Chesney M. Adherence to HAART regimens. *AIDS Patient Care STDs*, 2003;**17**:169–177.

23. Mills EJ, Nachega JB, Bangsberg DR *et al*. Adherence to HAART: a systematic review of developed and developing nation patient-reported barriers and facilitators. *PLoS Med*, 2006;**3**:e438.

24. 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;**64**:599–606.

25. Dejesus E, Young B, Morales-Ramirez JO *et al*. Simplification of antiretroviral therapy to a single-tablet regimen consisting of efavirenz, emtricitabine, and tenofovir disoproxil fumarate versus unmodified antiretroviral therapy in virologically suppressed HIV-1-infected patients. *J Acquir Immune Defic Syndr*, 1999;**2009**:163–174.

26. Cerdá JV, Gómez MC, Rodríguez IE *et al*. Preferences, satisfaction and compliance with antiretroviral treatment: ARPAS study (II). *Farm Hosp*, 2007;**31**:340.

27. Viciana P, Rubio R, Ribera E *et al*. Longitudinal study on adherence, treatment satisfaction, and effectiveness of once-daily versus twice-daily antiretroviral therapy in a Spanish cohort of HIV-infected patients (CUVA study). *Enferm Infecc Microbiol Clin*, 2008;**26**:127–134.

28. Sterrantino G, Santoro L, Bartolozzi D, Trotta M, Zaccarelli M. Self-reported adherence supports patient preference for the single tablet regimen (STR) in the current cART era. *Patient Prefer Adherence*, 2012;**6**:427–433.

29. Buscher A, Hartman C, Kallen MA, Giordano TP. Impact of antiretroviral dosing frequency and pill burden on adherence among newly diagnosed, antiretroviral-naïve HIV patients. *Int J STD AIDS*, 2012;**23**:351–355.

30. Nachega JB, Parienti J-J, Uthman OA *et al*. Lower pill burden and once-daily dosing antiretroviral treatment regimens for HIV infection: a meta-analysis of randomized controlled trials. *Clin Infect Dis*, 2014;**58**:1297–1307.

31. Llibre JM, Antela A, Arribas JR *et al*. Role of fixed-dose combinations of antiretrovirals in HIV-1 therapy. *Enferm Infecc Microbiol Clin*, 2010;**28**:615–620.

32. Walensky RP, Sax PE, Nakamura YM *et al*. Economic savings versus health losses: the cost-effectiveness of generic antiretroviral therapy in the United States. *Ann Intern Med*, 2013;**158**:84–92.