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ORIGINAL ARTICLE

Evolution of antiretroviral treatment adherence from 2000 to 2008☆

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Abstract
Objectives: To evaluate antiretroviral treatment adherence in the HIV patient cohort of our hospital and observe their evolution over a 9-year period, and to determine the individual pattern of adherence over time.
Methods: Descriptive study of the evolution of average annual adherence and the annual percentage of adherent patients greater than 95% from 2000 to 2008. We analysed the individual pattern of adherence over time and patients were classified as 'consistently adherent', 'consistently non-adherent', and 'fluctuating'.
Results: In the analysis of 577 patients, baseline adherence was significantly greater in naïve patients compared to those who were pre-treated.
Average annual adherence increased slightly and stayed at values around 95%. As with the percentage of patients with adherence greater than 95%, which increased from 64%in 2000 to 79% in 2008.
In terms of the individual pattern of adherence over time, of the 468 patients analysed, the majority (59%) were consistently adherent, 4% non-adherent, and the rest (37%) fluctuated in their adherence.
Conclusions: In our cohort, the overall adherence values remained steady over time and even show a positive trend, which is likely to be the result of systematic monitoring of adherence and implementation strategies to maintain adherence.

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PALABRAS CLAVE
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Terapia antirretroviral;
Síndrome de la inmunodeficiencia humana adquirida (sida);
Virus de la inmunodeficiencia humana

Evolución de la adherencia al tratamiento antirretroviral del 2000 al 2008

Resumen
Objetivos: Evaluar la adherencia al tratamiento antirretroviral en la cohorte de pacientes VIH de nuestro hospital y ver su evolución a lo largo de 9 años, así como conocer el patrón individual de la adherencia con el tiempo.
Métodos: Estudio descriptivo de la evolución de la adherencia media anual y el porcentaje anual de pacientes con adherencias superiores al 95%, desde el 2000 al 2008. Se analizó el patrón individual de adherencia con el tiempo y se clasificó a los pacientes en adherentes consistentes, no adherentes consistentes y fluctuantes.
Resultados: En el análisis de 577 pacientes, la adherencia basal fue significativamente mayor en los pacientes naive respecto a los pretratados.
La adherencia media anual aumentó ligeramente y se mantuvo en valores cercanos al 95%, al igual que el porcentaje de pacientes con adherencia superior al 95%, que aumentó desde el 64% en el 2000 al 79% en 2008.
En cuanto al patrón individual de adherencia con el tiempo, de los 468 pacientes analizados, la mayoría (59%) fueron adherentes consistentes, un 4% no adherente y el resto (37%) presentaban fluctuaciones en su adherencia.
Conclusiones: En nuestra cohorte los valores de adherencia global se mantienen con el tiempo e incluso presentan una tendencia positiva, resultado de una monitorización sistemática de la adherencia e implantación de estrategias dirigidas a mantener la adherencia.

Introduction

Antiretroviral treatment (ART) requires a high level of adherence by the patient to ensure its efficacy.[1] However, reaching a good level of adherence is not sufficient, as adherence must be maintained over time. Studies performed with the first high-efficiency antiretroviral treatments showed that adherence levels greater than 95% were needed,[2] although, according to new studies,[3] the level of adherence needed would be somewhat less stringent for non-nucleosides (NN) and boosted protease inhibitors (PI).

Adherence is conditioned by several different factors, among which the most prominent are adverse side effects, complexity of treatment, active consumption of drugs and/or alcohol, and mental illness.[4] The detection and correction of factors that could influence patient adherence should be an integral part of the follow-up protocol for these patients. In fact, several reviews have been published regarding methods for improving adherence.[5,6] To do so, routine monitoring of the level of adherence is essential, and all non-adherent patients must be identified.

Longitudinal studies examining adherence to ART treatment indicate that long-term adherence is difficult for most patients, even patients with an initial adherence of 100%.[7,8] In a study by Murphy,[9] which includes 231 adolescents, the mean percentage of adherence was 69%. However, with regard to the longitudinal adherence calculated in only 65 patients that were initially adherent, the mean time for loss of adherence was 12 months (95%CI: 9-15). The factors related to this loss were age and depression.

Other studies suggest that adherence diminishes with time, but these studies involve certain limitations, such as the length of follow-up, the number of patients, the methods used for measuring adherence, and the fact that many treatments used are not currently recommended.

Adherence has been monitored as a routine procedure since mid-1999 at the Galdakao-Usansolo Hospital, one year after the outpatient pharmaceutical care unit had been created. Adherence is calculated between checkups, and this information is given to clinicians during the medical appointment to aid decision-making. In 2000, a new adherence indicator was calculated: the mean annual adherence, which has been included as an indicator for quality control since 2003.

By systematically monitoring adherence, we are not simply interested in detecting non-adherent patients, but also want to know the mean adherence of our patients and to attempt to maintain it at a constant over time. To do so, a series of interventions have been performed during this time period,[10] through which a new methodology has been established, which pays closer pharmaceutical attention to non-adherent patients. Furthermore, follow-up is maintained even with irregular patients through appointments in the infectious disease department.

The objective of this study is to evaluate the tendency for adherence to ART treatment in the cohort of HIV patients at our hospital during a 9-year period. We also attempt to understand individual patterns of the evolution of adherence over time.

Method

We performed a descriptive study on the evolution of patient adherence during a 9-year period, from 1 January 2000 until 31 December 2008. We examined all HIV patients over 18 years of age receiving ART treatment at the

Galdakao-Usansolo Hospital. We excluded those patients with no data regarding adherence, which mainly occurred when the duration of treatment was less than 3 months.

Drugs are dispensed on a monthly basis at our hospital, and mean annual adherence is measured over 12-month intervals, following the calendar year. Adherence was calculated using pharmacy dispensing records (PDR),[11] and adherence was defined as the number of days of ART dispensed divided by the number of days of the interval being studied, expressed as a percentage.

We analysed the following baseline variables: sex, origin, age, and previous experience with antiretroviral treatment (naive or pre-treated) at the start of the follow-up period. We used the chi-square test for analysing qualitative variables, and the Student's *t*-tests for quantitative variables.

In the assessment of annual adherence, we only considered those patients had been under treatment for at least 3 months during that year, and we excluded patients who had suspended treatment, been transferred between health centres, had abandoned treatment, and deaths.

We calculated mean annual adherence along with standard deviation (SD), the percentage of patients with optimal adherence (greater than 95%), and patients with adherence greater than 90% Adherence was considered as a continuous quantitative variable for calculating mean annual adherence, and as a dichotomous variable (adherent or non-adherent) to calculate the number of patients with optimal adherence in the statistical model.

The mean follow-up period for patient adherence was defined as the years with adherence data, excluding those patients who had suspended treatment, been transferred or abandoned treatment, as well as those that died during the study. We calculated these values as a median and interquartile range (IQR).

We analysed the individual patterns of adherence over time and classified patients as: 'consistently adherent' (CA), when adherence was equal to or greater than 90% during the follow-up period (those with greater than 95% adherence were considered as cases of 'excellent adherence'); 'consistently non-adherent' (CNA), when adherence was less than 90%; and 'fluctuating' (F), when the patient did not consistently fall within either of the other two groups. For this portion of the study, we only included patients with a follow-up period equal to or greater than 3 years.

Results

From the initial assessment of 608 patients on antiretroviral treatment, we selected 577 patients with adherence data, 72% of which were men, with a low percentage of foreign patients, as is summarised in Table 1. The mean patient age was 38.2 years, and 27% of the study population were naive to antiretroviral treatment before the start of the monitoring period. Mean adherence was 93% (SD: 9.9).

No differences were observed in baseline patient data, except for age at the start of treatment, which was significantly lower for women (36.2 years) than for men (38.9 years) (difference of 2.7 years, 95% CI: 4-6.8 years; $P<.0001$).

As the table indicates, no differences were observed between adherent and non-adherent patients with regard to patient origin and sex. Differences were observed, however, when considering the age of the patient at the start of treatment, such that adherent patients were significantly older than non-adherent patients. Lastly, adherence was also significantly higher in the naive patient group when compared with pre-treated patients.

The mean duration of the adherence follow-up period per patient was 3 years (IQR: 3-9 years). When considering overall adherence values, evolution between 2000 and 2008 was positive, maintaining high values, from 92.9% in 2000 to approximately 95% since 2005 (Table 2).

Figure indicates the progression of the percentage of patients with optimal adherence (equal to or greater than

Table 1 Baseline socio-demographical characteristics

	Total No.=577	Adherent patients* No.=383	Non-adherent patients No.=194	*P* value
Sex, %				.845
Women	28.1	67.3	32.7	
Men	71.9	66	34	
Origin, %				.232
European	96	66.8	33.2	
African	2.6	75	25	
South American	1.4	46.7	53	
Previous treatment, %				<.001
Naive	27.2	79.6	20.4	
Pre-treated	72.8	61.4	38.6	
Mean age at start of treatment (SD)	38.2 (7.3)	38.6 (7.5)	37.4 (6.7)	.04

SD indicates standard deviation.

*Patients are considered adherent when adherence was equal to or greater than 95%

Table 2 Evolution of mean annual adherence

	2000	2001	2002	2003	2004	2005	2006	2007	2008
No. of patients	336	369	373	367	383	380	398	401	429
Mean % (SD)	92.92 (10.7)	93.59 (10.18)	93.34 (10.27)	93.13 (11.12)	93.87 (10.55)	94.60 (10.86)	95.68 (8.58)	96.43 (7.56)	95.45 (9.79)

SD indicates standard deviation.

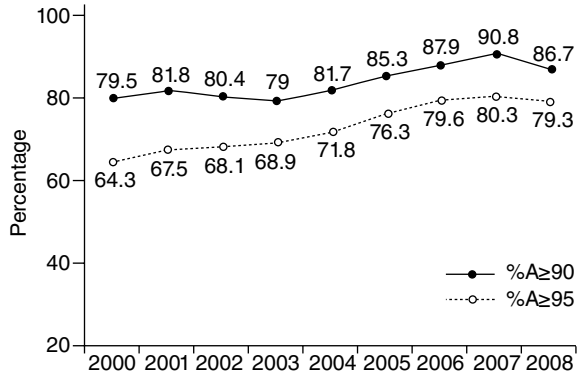

Figure 1 Percentage of patients with adherence greater than 90% and 95%. %A≥90: % of patients with adherence greater than 90%; %A≥95: % of patients with adherence greater than 95%.

95%), which increased from 64% in 2000 to 79% in 2008. The number of patients with adherence greater than 90%also increased during this period, but less so.

We analysed the individual patterns of 468 patients with a follow-up period equal to or greater than 3 years, which constituted 81% of all patients. Fifty-nine percent of the patients (278 patients) were CA, whereas only 4% (19 patients) were CNA, and the rest of the patients (37%) fluctuated in terms of adherence. 73% (204/278) of CA patients consistently maintained adherence at more than 95% Adherence in these patients was considered as 'excellent'.

For the group of patients where consistency of adherence was evaluated, 9.8% abandoned treatment at some point during the follow-up period, most of which were in the group of patients with fluctuating adherence.

Discussion

The mean annual adherence values in our population were high, close to 95%, and similar to previously published data,[12] including studies in the Spanish population.[13]

At our centre, we have kept annual records of mean adherence and the number of patients with optimal adherence throughout the 9-year period, and have compared it with other studies, observing a decrease in adherence over time.[14] In a cohort of 903 naive patients[15] that started ART treatment between 2000 and 2005 and with a median follow-up time of 33 months, the mean rate of adherence decreased from 79%at 6 months after starting treatment to 72%during the period of 24-30 months. Cooper et al[16] also observed the percentage of naïve patients with adherence below 95%increased after 6 months of follow-up, yielding an inverse relationship between the increased number of HIV-associated symptoms and treatment, and adherence.

The analysis of the individual patterns of adherence indicate that the majority of our patients maintained optimal levels of adherence during the follow-up period, whereas only 4% consistently did not adhere to the treatment, and over one third fluctuated between optimal and sub-optimal adherence. Similar results were observed in the study by Schonnesson et al,[17] in which 61%of patients maintained 100%adherence during 24 weeks of follow-up, one third communicated non-adherence in at least one visit during the follow-up, and the cases of consistent non-adherence were minimal.

In our cohort, there was a slight increase in adherence, probably as the interventions were designed to correct lack of compliance,[18] and due to other factors such as the progressive simplification of ART treatments and progressive reductions in drug and alcohol abuse. Similarly, in the study by Ostrop,[19] the percentage of patients with adherence greater than 80% increased following an intervention, moving from 75% in the retrospective phase to 84% in the prospective phase.

One of the limitations of our study is that we only evaluated patients that had collected their prescriptions during a minimum of 3 months, which was conditioned by the method we used for measurement. This method had the advantage of being useful in situations where medication pickup is centralised in a single pharmacy, as occurs in Spain, where patients obtain their medications from the hospital Pharmacy Department. In a survey performed among 68 Spanish hospitals, PDR were the most commonly used method for measuring adherence,[20] and this method has been used in different studies on HIV populations.[21,22]

Another important limitation of our study was the lack of knowledge regarding the impact of adherence on viral load, which is a efficacy-related variable. In this respect, Gardner[23] suggested that reduced adherence is frequent and has a significant impact on the durability of antiretroviral treatment, such that sub-optimal adherence is strongly associated with reduced duration of treatment.

Lastly, we did not take into account those factors related to the loss of adherence in our study. In other studies, the loss of adherence over time has been related to the use of alcohol and drugs, age, economic problems,[24] and depression, among others.

In conclusion, adherence values remained stable over time for our cohort of patients, and it could even be said that they showed a positive tendency. Even so, we must not forget that 20%of our patients have sub-optimal adherences, and that a significant number of patients abandon treatment.

Without a doubt, we must routinely and continuously monitor patient adherence to pharmacological treatment in order to detect non-adherent patients and develop strategies for improving adherence, and to ensure that patients remain at optimal levels. We must also not forget the failure to comply with follow-up appointments and those patients that abandon treatment. Different strategies should therefore be designed for each scenario, such as strategies for maintaining optimal adherence, strategies for increasing adherence, and strategies to ensure that the patient remains within the health system.

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