

# GESIDA/SEFH/PNS recommendations for improving adherence to antiretroviral therapy

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**The main objective of HAART is to achieve complete and lasting suppression of viral replication. However, when therapeutic drug levels are low, HIV can replicate and develop resistance. This can lead to treatment failure, transmission of resistant strains and, therefore, inappropriate use of financial resources. In order to achieve adequate therapeutic drug levels, treatment must be strictly adhered to. The factors that influence adherence and methods of evaluation are reviewed and possible strategies for intervention which should be undertaken by a multidisciplinary team of physicians, pharmacists, nurses, psychologists and other support personnel are recommended. Initiation of HAART is not usually an emergency measure. For this reason it is very important to prepare the patient and identify non-adherence factors in order to correct them. Once HAART is ordered, it is very important to offer information on the prescription and dispensing of drugs. During therapy it is necessary to actively**

**follow up all patients on HAART. In order to make therapeutic decisions the patient's drug adherence rate must be known. Several methods of calculating the drug adherence rate are recommended, the most common being the patient interview, patient questionnaire, refill count, pharmacy visit rate and evolution of the patient's viral load. In order to obtain this information, very good communication is necessary among all the people involved in the care of HIV-infected patients. If non-adherence is detected, it is necessary to initiate corrective strategies and, if they fail, in some cases, it might be necessary to discontinue HAART. The potential benefits of adherence programs can justify the financial outlay on human and hospital resources.**

**Key words:** HIV. HAART. Adherence programs.

Recomendaciones GESIDA/SEFH/PNS para mejorar la adherencia al tratamiento antirretroviral

**El objetivo del tratamiento antirretroviral es la supresión profunda y duradera de la replicación viral. Las especiales características virológicas del virus de la inmunodeficiencia humana (VIH) determinan que cuando existen concentraciones**

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subterapéuticas de los fármacos el VIH puede multiplicarse y desarrollar resistencias. Esto puede justificar el fracaso terapéutico, la posible transmisión de cepas resistentes y la utilización inadecuada de los recursos económicos. Por tanto, uno de los factores más importantes para conseguir unos niveles terapéuticos adecuados es la correcta adherencia terapéutica. En esta revisión se analizan los factores que influyen en la adherencia, los métodos de evaluación y se recomiendan las posibles estrategias de intervención y de actuación de un equipo multidisciplinario que debe ser integrado por médicos, farmacéuticos, enfermeras, psicólogos y personal de soporte. El inicio del tratamiento antirretroviral no es habitualmente urgente. Dada la importancia que tiene realizar de manera correcta este primer tratamiento conviene, antes de iniciar la terapia, preparar al paciente, tratar de identificar las potenciales situaciones concomitantes que puedan dificultar una correcta adherencia y corregirlas. Si se decide que el paciente inicie el tratamiento es imprescindible que en el momento de la prescripción y la dispensación de los fármacos se ofrezcan una información detallada, soporte y accesibilidad en todos los aspectos relacionados con el tratamiento. Durante éste, la evaluación de la adherencia es imprescindible y deberá tenerse en cuenta en la toma de decisiones terapéuticas. Al no existir un único método fiable, recomendamos utilizar varias técnicas como la entrevista y el cuestionario estructurado, el recuento de la medicación sobrante y la asistencia a las citas de dispensación de fármacos junto con la evolución clínica y analítica del paciente. Para ello es indispensable que exista una buena coordinación entre todos los estamentos implicados. Si se detecta una falta de adherencia debe intervenir de forma activa para corregirla, y en situaciones extremas puede valorarse la suspensión del tratamiento. Los beneficios que aporta un programa para mejorar la adherencia justifica disponer de suficientes recursos económicos, humanos y de infraestructura que faciliten el desarrollo de estas actividades.

**Palabras clave** HIV. VIH. Tratamiento antirretroviral. Adherencia.

## Introduction

In the last few years, there have been enormous advances in the field of antiretroviral therapy. This has led to a reduction in pro-

gression of the disease, an improvement in survival and a drop in the number of opportunistic infections as well as admissions of HIV patients<sup>1</sup>.

The objective of antiretroviral therapy is the deep and lasting suppression of viral replication<sup>2</sup>. Knowledge of the mechanisms of resistance suggests that the persistence of replication in the presence of antiretrovirals invariably leads to the selection of resistant strains. Both the least active therapies and incorrect adherence to treatment create the conditions for the selective pressure which increases the possible emergence of resistant mutations<sup>3,4</sup>. Several factors may have a negative influence on achieving the desired objectives, such as clinical stage, infecting viral strain, previous treatment history, baseline viremia and pharmacokinetic problems, but the most important of all is incorrect adherence to treatment. Adherence to therapy is a powerful predictor of response both in the context of clinical trials and in cohort studies<sup>5-7</sup>. Given this extremely important role, the lack of adherence has been described as the «Achilles heel» of antiretroviral therapy<sup>8</sup>.

The terms «adherence» and «compliance» are often used indistinctively. In the early days, only the term «compliance» was used to define the correct taking of medication. However, some authors prefer the term «adherence», because they think it defines an attitude of the patient, and reflects a commitment to the medication prescribed by the physician with an active participation in the choice and maintenance of the therapeutic regimen<sup>9,10</sup>. Incorrect adherence or compliance includes aspects such as forgetting to take the medication, not respecting the correct administration frequencies and intervals, not adjusting to the requirements of administration with respect to meals and other circumstances.

The rates of compliance reported in chronic diseases range from 0 to 90%, with the average at 50%<sup>11</sup>. Several studies consider compliance of 80% of prescribed medication acceptable, and thus, in the first studies on adherence in HIV-infected patients treated with zidovudine, the same criteria were followed<sup>12,13</sup>. However, in the protease inhibitor treatment stage, when degree of adherence is related to degree of effectiveness, it is obvious that short periods of low compliance or rest from medication are associated with increa-

sed viremia<sup>14</sup> and that only adherence of more than 90% of the prescribed doses, respecting the intervals between doses and the relationship with food, gave satisfactory results<sup>15</sup>. One study established a clear relationship between degree of compliance and effectiveness. Thus, undetectable viremia was obtained in 81% of patients with compliance above 95%, in 61% with compliance of 90%-95%, in 50% with compliance of 80%-90%, in 25% with compliance of 70-80% and only in 6% who complied with less than 70%<sup>16</sup>.

The degree of compliance necessary to obtain the maximum benefit will depend on the regimen used, the pharmacokinetics and pharmacodynamics of each of the agents used and the factors related to the infecting virus and the patient. Drugs with a longer half-life allow better-spaced dosing intervals and have a greater «period of tolerance», which is obtained by subtracting the duration of the drug's action from the dosing interval<sup>17</sup>. Table 1 summarizes the pharmacokinetic characteristics of antiretroviral drugs.

HIV infection therapy incorporates all the factors which make adherence difficult: more than one drug, more than one administration per day, adverse effects and prolonged treatment. Therefore, reaching the objective of optimum compliance represents a real challenge for the patient and healthcare personnel. In studies carried out in Spain, the percentage of patients who correctly adhered to HAART, that is, more than 80% of the prescribed dose, ranged from 56% to 83%<sup>18-20</sup>.

The importance of reaching optimum compliance is mainly due to the potentially fatal consequences of non-compliance, both with regard to its efficacy and to facilitating the possible development of resistance. The latter, owing to the appearance of cross-resistance among drugs which act on the same target in the viral replicative cycle means that, in patients who have developed resistance due to sub-optimal treatment, the possibilities of efficacious therapy are very limited. This point, which is important for the individual, takes on enormous importance at group level, since the transmission of multiresistant strains to the community can minimize the huge advances made with HAART<sup>21,22</sup>.

Another aspect, which should not be forgotten, is the financial cost. The cost of antiretrovirals in Spain stands at about 6,000-12,000 euros per patient per year (average 9,000 euros).

Calculating that in Spain there are a total of 50,000 patients in treatment, the annual antiretroviral budget can be as high as 450,000,000 euros, a figure which stresses the need for correct use of this medication. In view of this, and starting from a good adherence rate in 50% to 70% of patients, the value of medication dispensed to non-adherers could drop to 30 billion pesetas per year. In a society such as ours, where resources are limited and where budgetary cutbacks are applied to the population in general, it is necessary to establish programs which guarantee the correct use of antiretroviral drugs. Consequently, the resources used to finance compliance improvement programs are ridiculously small in comparison with those which are wasted as a consequence of low adherence<sup>23,24</sup>.

The approach to this problem must be multidisciplinary. The intervention of different departments, governmental and non-governmental institutions, the pharmaceutical industry and support groups, can all help reach this goal. This document puts forward a series of recommendations to be carried out in the healthcare environment.

## Factors which influence adherence

Factors associated with adherence can be attributed to the individual, the disease, the medication or to the healthcare team. The diagram in figure 1 shows how the different factors interact.

### Individual

Demographic characteristics (age, sex, race, education, occupation), as well as culture and stable economic situation, do not predict an individual's degree of adherence. However, elderly patients have been observed to adhere better to treatment, with the exception of those over 75 in whom comorbidity worsens compliance.

A fixed address and social support with a structured family or friends are factors which facilitate adherence<sup>9</sup>. This brings to mind the homeless, marginal groups and drug users, whose situation is extraordinarily complex. In cross-sectional studies carried out on active addicts, 49%-60% were not receiving highly active therapy and only

TABLE 1. Pharmacokinetic characteristics of antiretroviral drugs

Medication	Adult dose (oral)	Total no. units per day (adults)	Bioavailability	Plasma half-life	Intracellular half-life	Meals	Metabolism	Elimination
Abacavir	300 mg/12 h	2	76-100% (animals)	0.8-1.5 h		With (out) meals	Liver	Kidneys 11%-15% unaltered
Didanosine <sup>a</sup> (ddI)	> 60 kg: 200 mg/12 h 400 mg/24 h < 60 kg: 125 mg/12 h 300 mg/24 h	3 or 4	40%	0.5-1.5 h	25-40 h	Without meals	Liver 50%	Kidneys 50% unaltered
Stavudine <sup>a</sup> (d4T)	> 60 kg: 40 mg/12 h < 60 kg: 50 mg/12 h	2	84-88%	1.1-1.5 h	3.5 h	With (out) meals	Liver 55%	Kidneys 45% unaltered
Lamivudine <sup>a,b</sup> (3TC)	> 50 kg: 150 mg/12 h < 50 kg: 2 mg/kg/12 h	2	82%	5-7 h	10-15 h	With (out) meals	Liver 5-10%	Kidneys 70% unaltered
Zalcitabine (ddc)	0,75 mg/8 h	3	> 80%	1-3 h	7-10 h	With (out) meals	Hardly any liver metabolism	Kidneys 75% unaltered Stool < 10%
Zidovudine <sup>a,b</sup> (AZT)	200 mg/8 h 250 mg/12 h 300 mg/12 h	2-6	60-70%	1 h	3 h	With (out) meals	Liver	Kidneys 90% (15% unaltered)
Indinavir	800 mg/8 h	6	30-60%	1.5-2 h		Without meals or with a light meal	Liver	Kidneys < 20% Stool 83%
Nelfinavir <sup>a</sup>	750 mg/8 h 1,250 mg/12 h	9-10	78%	3.5-5 h		With meals	Liver	Kidneys 1-2% Stool 87% (22% unaltered)
Ritonavir <sup>a</sup>	500 mg/12 h (start) 600 mg/12 h	Oral solution	70-100% (animals)	3-5 h		With meals	Liver	Kidneys 12% Stool 86%
Saquinavir	600 mg/8 h	9	4%	1-2 h		With meals	Liver	Kidneys 1-3% Stool 85%
Delavirdine	400 mg/8 h	12	85%	2-11 h		With (out) meals	Liver	Kidneys 51% (< 5% unaltered) Kidneys 44% Stool 66%
Efavirenz	600 mg/24 h	3	66%	40-55 h		With (out) meals	Liver	Kidneys 80% Stool 10%
Nevirapine	200 mg/24 h* 200 mg/12 h 400 mg/24 h	2	> 90%	25-30 h		With (out) meals	Liver	Kidneys 80% Stool 10%
Hydroxyurea	500 mg/12 h	2	100%	2-3 h		Without meals	Liver	Kidneys

\*First 14 days; <sup>a</sup> available oral solution in the market; <sup>b</sup> at present in the same dosage form exist the association of AZT and SCT at 300 and 150 mg doses, respectively.

14%-17% were<sup>25,26</sup>. In order to improve acceptance and compliance among these patients we must adopt a multifactorial and multidisciplinary approach<sup>27,28</sup>.

Psychological factors also influence adherence. Anxiety and depression worsen adherence. In a study carried out on patients who were receiving zidovudine, adherence fell from 81% to 52.6% according to the absence or presence of these factors<sup>29</sup>. Alcoholism was identified as a factor related to poor adheren-

ce<sup>9</sup>. Given the high prevalence of comorbidity in HIV-infected patients, it is necessary to consider psychiatric and psychological intervention as an important part of normal care.

Patient attitude and beliefs with respect to medication, the illness and the care team are essential factors when accepting the proposed treatment and carrying it out correctly. The perception of potential benefit is fundamental in chronic diseases with an asymptomatic course<sup>9</sup>.



care team with no clear references for the patient, can make adherence difficult. Probably the most important factors are the supply of detailed and authentic information and the taking of joint decisions in a framework of mutual confidence<sup>9,24</sup>.

The availability of specially motivated personnel with experience and specific knowledge is essential to achieve optimal quality in care.

Given the complexity of the problem, the care team should be multidisciplinary, that is, it must bring together the work of physicians, nurses, hospital pharmacies, social workers, psychologists and other institutional services.

## Adherence evaluation systems

There are several systems for evaluating adherence to treatment. However, given that none of the existing methods is 100% reliable, it is necessary to combine several to obtain information on the real situation with the greatest degree of accuracy possible<sup>35-37</sup>.

Measurement of compliance must reflect the administration of medication both in clinical units and in time, as well as measuring whether or not objectives have been reached (e.g., undetectable viremia). Compliance should be expressed as a rate of overall adherence and if possible it should be measured for each of the drugs in the therapeutic regimen. It is useful to express this rate in one of the following three ways: as a percentage of doses taken, as a percentage of days with the correct number of doses or as a percentage of doses taken at the correct time.

Quantification of compliance is extremely important. It may be expressed as a continuous or dichotomic variable and the choice of the type of measure depends on several factors, the reliability of the results of measurement on one hand, and on the other, the relationship between dose and response. Although the validity, sensitivity, specificity or representativeness of these methods of measurement are not ideal, it seems to have been demonstrated that a «90%» cut-off point is significantly related to virological response<sup>15,16</sup>. It seems logical to establish this limit as a value which allows a patient to be classified as a complier (>90%) or a partial complier (<90%).

The methods for evaluation of adherence are either direct or indirect.

### Direct methods

These involve determining the levels of drug present in organic liquids such as plasma, saliva or urine. Although it is one of the most reliable methods, it has the disadvantage of interindividual variability in the pharmacokinetic behavior of some drugs, as well as the possibility of plasma concentrations altered by the appearance of medication interaction. Furthermore, finding correct levels of drug in plasma on the day of sample extraction does not guarantee that compliance is continuous. The method is expensive and not easy to apply routinely.

### Indirect methods

These are less reliable as the final evaluation is influenced by several variables, but they have the advantage that they are easy to apply in daily practice. These methods are:

1. *Interview* with the patient, based on simple questions and in a framework of mutual trust which leads to sincerity and precision about how medication has been taken (frequency, errors, omissions and reasons)<sup>38</sup>. To apply this method it is necessary to have certain communications skills. It is a subjective method, with a positive predictive value in non-complying patients.
2. *Structured questionnaire*. This involves asking the patient to fill in a questionnaire on adherence. In this case, the patient gives the information, which is subjective, but on the other hand, the data obtained can be processed more quantitatively than in the interview. At present there is no universally validated and accepted questionnaire. This is undoubtedly an area worthy of further study.
3. *Programmed attendance at dispensing*. This is a predictive method of compliance, although it does have exceptions. The fact that a patient arrives on time for a medical visit and appointments with the pharmaceutical service leads us to believe that the patient is adhering well. On the other hand, not attending when due to collect medication is a sign of poor compliance. However, it must be remembered that, exceptionally, some patients may obtain their supply from another hospital from time to time or share medication

with another member of the family.

4. *Surplus medication count.* This involves counting the number of units of medication left in the container of the pharmaceutical specialty the patient is taking. If the date of initiation of treatment is known, the theoretical number of units taken can be calculated by the difference. This method has the disadvantage that if the patient knows that there is going to be a count, he can manipulate the contents of the container. One system would involve a surprise count in the patient's home.

$$\% \text{ compliance} = \frac{\text{Units dispensed} - \text{surplus units}}{\text{Theoretical units taken}} \times 100$$

There is another very simple and easy-to-apply method which involves giving the patient a diary to record the medication he/she takes or to record the surplus medication before each administration. In addition to removing the responsibility for the count from the pharmacy service, this method can serve as a support element in improving adherence.

5. *Electronic monitoring.* This method is more sophisticated. It involves using MEMS<sup>®</sup> devices, which, by means of an electronic lid system, record the date and time the container is opened. Thus, it is possible to know the frequency with which the patient takes the medication and if doses are omitted. However, this allows only one inference as it indicates the opening of the container, but not whether the patient took the medication or whether the dose was correct. Other drawbacks, such as the size (with the result that some patients do not want to carry them) or the price, force them to be reserved for clinical trials or research studies<sup>39,40</sup>.
6. *Clinical evolution and analytical data.* Specific clinical and/or laboratory data can lead to suspicion of poor adherence. Thus, for example, in patients treated with zidovudine there is an increase in the mean corpuscular volume. In patients in whom this parameter is not altered, low adherence should be sus-

pected, as well as in those in whom clinical, virological or immunological progression is observed, but always bearing in mind that adherence is not the only factor which can intervene in treatment failure.

## Strategies for improving adherence to antiretroviral treatment of the care team

Early identification of poor adherence can help to prevent unnecessary changes in treatment. It is essential to be able to distinguish between poor adherence and the lack of intrinsic response to medication.

Table 2 describes some of the main causes of non-compliance and the different techniques and tools for solving the problem. Intervention strategies can be classified into three types. The first involves acceptance by the healthcare professional of the existence and importance of therapeutic non-compliance. The second type of strategy should be aimed at the patient and is focused on communication and psychosocial support. The third focuses on education and motivation of the healthcare team itself.

Each hospital should adapt to its healthcare reality according to the number of patients it attends, human resources and support services. In principle, the healthcare team has three basic cores: the prescribing physician, the pharmacist who dispenses the drugs and patient care support, made up of the nursing staff and, where possible, psychologists and psychiatrists. Coordination with primary care, social services and NGOs should be a desirable objective in overall care of the HIV patient.

### Role of the physician. Recommendations for the prescription of medication

Before beginning prescription, the physician must consider the basic premise that the best opportunity for obtaining maximum suppression of viral load lies in the first treatment.

Furthermore, initiation of antiretroviral treatment is rarely an emergency. Only in the cases of primary infection, post-exposure prophylaxis or as prophylaxis of vertical transmission during delivery, must treatment be initiated quickly. It is obvious that the situation differs with the clinical situation and de-

TABLE 2. Potential causes of non-adherence and possible strategies of intervention

Potential causes of non-adherence	Possible intervention
<b>Non-acceptance</b> Rejection of diagnosis Rejection of treatment (beliefs and attitudes: mistrust, hostility, fear, fatalism, invulnerability, incapacity)	Analyze the patient/healthcare professional relationship and improve the effectiveness of the relationship Negotiate and agree on the therapy program Encourage the perception of indicators which show the need to apply treatment Inform on risks and benefits of treatment
<b>Non-comprehension</b> Insufficient understanding of the illness and its treatment Insufficient understanding of the risk/benefit relationship  Reason for dosing and compliance	Improve patient/healthcare professional communication Information referring to the illness and treatment, reason for dosing, risk of non-compliance
<b>Problems with the medication</b> Adverses effects, size and palatability of the drugs, number of daily doses	Modify and simplify therapeutic regimen Special techniques for taking medication Help to develop reaction mechanisms (e.g., anticipation and management of adverse effects)
<b>Forgetfulness and barriers</b> Lapses due to lifestyle, anxiety, lack of motivation, poor integration of medication to lifestyle, etc.	Associate administration with daily routine Special techniques and aids for compliance (medication diaries, alarms, etc.) Alternative dosing. Motivation and persuasion Family support, social support (friends, careers, social services)

gree of acceptance of each patient, thus, in an asymptomatic patient with a relatively intact immune system, the start of treatment can be postponed for a few months, during which any concomitant pathology (alcoholism, depression, drug addiction) can be solved and during the following visits the physician will insist on the need to initiate treatment. In a symptomatic patient, however, the preparation of the patient must be rapid and, probably, if he/she accepts the treatment, the approach to comorbidity must be made on initiating the regimen.

In general, start of antiretroviral therapy while in the hospital is not recommendable, with the exception of those cases in which the pathology that led to admission does not have an effective treatment (cryptosporidiosis, progressive multifocal leukoencephalopathy). Furthermore, with patients who are already in treatment, it is necessary to continue therapy during hospitalization if their clinical condition permits it.

It is very difficult to predict the degree of adherence of an individual before starting therapy, since, moreover, physicians and patients may have different perceptions of the difficulties involved in carrying out a regimen<sup>41</sup>. It is therefore preferable to prepare the patient before beginning treatment, if necessary in two or more visits, and verify

whether he/she can really face the difficult task of adhering to therapy<sup>27</sup>.

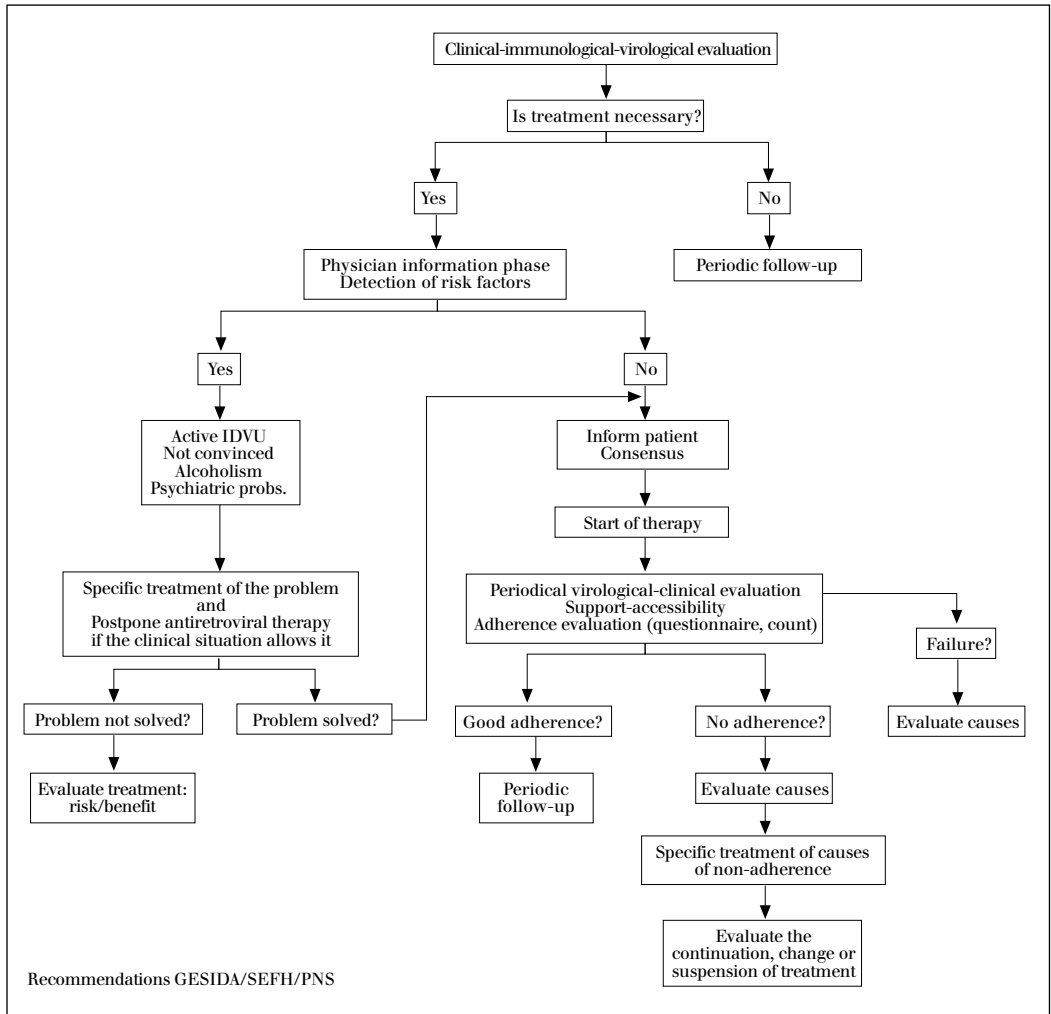
In the case of a patient who repeatedly adheres poorly, when all improvement strategies have been exhausted and treatment is seen to be ineffective, it may be wise to consider temporary suspension (see table 2 and figure 2). However, if possible, supervised administration with the help of family members or friends, non-governmental organizations or centers with methadone programs for patients who are included in them<sup>42,45</sup> should be attempted first.

Once a physician knows the state and clinical condition of the patient, the prescription of antiretroviral drugs passes through three different phases<sup>8,44</sup>. Table 3 summarizes the main characteristics of these phases and figure 2 gives a schematic representation of behavior in prescribing treatment.

#### *Information phase*

Throughout this phase, the physician must get to know the patient's family, social and work situation, his/her lifestyle, schedules and daily activities, psychological situation (anxiety, depression) and attitudes or beliefs concerning the disease and its treatment.

It is necessary to determine the virological, immunological and clinical situation, as well as history of previous treatment and whether



**Figure 2.** Algorithm for acting on starting and maintaining antiretroviral treatment. IDVU: intravenous drug user; GESIDA: Grupo de Estudio de Sida; SEFH: Sociedad Española de Farmacia Hospitalaria; NAP: National AIDS Plan.

there have already been problems with adherence.

It is essential to know the non-HIV-related pathology and drugs or substances that the patient is taking, either continually or sporadically, in order to take possible pharmacological reactions into account.

Other points to be considered are the preferences and difficulties which the patient may express as treatment progresses: number of pills per day, number of doses per day, administration schedule, relationship to meals, characteristics of the medication (taste, size), etc. Given the possibility of starting

alternative therapies, it is worthwhile asking the patient his/her preferences concerning these alternatives.

The patient, for his/her part, should know his/her immunological, virological, clinical situation, the dynamics of the infection, the objective of treatment, dosing, treatment alternatives, the reasons for and importance of adherence, potential adverse effects and the management thereof.

The information given will depend on the physician, with the support of nursing staff, and this can be complemented by written material.

TABLE 3. Recommendations for prescription

<b>Information phase</b>
Identify possible patient risk factors for adherence
Discover the family, work, social situation
Ascertain concomitant pathological and psychological situation (drug addiction, alcoholism)
Ascertain preferences and difficulties for treatment
Explain the objectives, reason for dosing, potential adverse effects of treatment
Offer possible treatment alternatives
Stress the importance of adherence in the efficacy of treatment
<b>Consensus and commitment phase</b>
Adapt treatment to patient's daily life
Agree on the medication, doses and regimen with the patient
Postpone treatment until consensus and commitment have been obtained from the patient
Deal with concomitant situations (depression, anxiety, alcoholism, drug addiction)
Request patient commitment in adherence to treatment
<b>Support and maintenance phase</b>
Evaluate adherence to treatment
Ascertain the problems and offer solutions (adverse effects, relationship with meals, timetables)
Accessible care (telephone, outpatient clinic, external consultation)

During this phase it is necessary to stress the importance of correct adherence to treatment and, if it is the case, stress that the first treatment can be decisive.

#### *Consensus and commitment phase*

Using the information obtained during the first phase, which ideally should be followed by a period of reflection, the patient and physician reach a consensus on the therapeutic regimen.

The treatment regimen must be individualized according to the habits and needs of the patient. It is important to adapt the treatment to the daily life of the patient, by trying to have medication become just another part of the daily routine<sup>45,46</sup>.

Treatment should be optimal from the beginning. Trial suboptimal treatments are not recommended.

The patient must show his/her commitment to continue with the chosen treatment in each of the terms agreed with the physician (medication, dose, regimen and form of administration).

In patients who are reluctant to take medication, an attempt must be made to try and convince them and obtain a change of attitude towards therapy. It is only recommended to start therapy with convinced patients for whom a consensus and commitment to treatment have been reached.

The prescription should be written in clear detail, including dose, administration timetable and relationship with meals. It must be confirmed that the patient has understood the written regimen.

For some patients, medication diaries, time reminders (alarms) and suitably individualized stocks may be useful<sup>8,47</sup>.

Additionally, in patients who have difficulty understanding or managing the medication, it is necessary to request the support of the family or people close to the patient<sup>8</sup>.

#### *Maintenance and support phase*

Once the program has started, patient follow-up requires correct scheduling of control visits.

In patients who are starting or changing treatment, the first control visit must be programmed for two weeks or, at most, one month after starting in order to verify compliance and tolerance, and if applicable, the necessary adjustments must be made.

In patients who are already in treatment, scheduled visits should be more or less frequent according to patient needs (clinical or adherence). At each visit, adherence is evaluated on the basis of a questionnaire (table 4 proposes a questionnaire which must be

TABLE 4. Simplified adherence questionnaire

	Yesterday	The day before yesterday	During the previous five days
Did you forget to take a tablet?	Yes/no	Yes/no	1 day-2 or more days
Did you forget any dose of all the tablets	Yes/no	Yes/no	1 day-2 or more days
Did you take a dose or a tablet outside the timetable	Yes/no	Yes/no	1 day-2 or more days
Did you take any tablet or all those of the doses without realizing that you had to do so with or without meals	Yes/no	Yes/no	1 day-2 or more days

4 «no» answers: suspect good adherence; only 1 «yes» answer (1 day): suspect good adherence; only 1 «yes» answer (2 or more days): suspect poor adherence; 2 «yes» answers (2 or more days): suspect poor adherence; 3 «yes» answers (2 or more days): suspect poor adherence; 4 «answers» (2 or more days): suspect poor adherence. If poor adherence is suspected, determine causes: simple forgetfulness, adverse effect, confusing instructions, problem with meals, change in habits (holidays, weekend).

validated in future research) and the patient is told of the immunological and virological advances achieved, insisting that in spite of such advances, compliance may not be relaxed. The purpose of evaluation is not to judge, but to try to solve possible problems. It is of interest to find out the reasons for non-compliance in order to deal with them properly.

Changes in routine (holidays, weekends) must be planned together, emphasising the need to avoid «treatment holidays».

It is important for the patient that his/her physician or care team be available as often as possible and that they be easily accessible to solve any doubts or problems which might emerge with medication.

### **Role of the pharmacist. Recommendations for dispensing medication**

After prescription, the pharmacy service can act on patients through dispensing, and carry out all the activities included in the area of «pharmaceutical care», which support and assist with questions concerning the drug therapy of the patients attended<sup>44,48-51</sup>. These activities are summarized in table 5.

#### *Pharmaceutical care process*

This section describes the four stages involved in the process of «pharmaceutical care» of HIV-infected outpatients who are served by the pharmacy service or the outpatient pharmacy unit.

*Introduction stage.* In this first stage, which coincides with the first visit, the pharmacist, as well as introducing him/herself to the patient, informs the patient of the procedure to be followed in the future for acquiring medication. Similarly, he/she insists on the bene-

fits stemming from the availability of this service and informs the patient of the importance of adhering to the treatment prescribed by the physician. The main objective of this first stage is for the patient to identify the pharmacist as a professional who is understanding and helpful in areas related to the illness and, above all, to the key factor of the illness, which is drug therapy<sup>52</sup>.

The pharmacist must be able to communicate and express him/herself well. He/she must be accessible, transmit trust and confidence, and keep up on the drug therapy of these patients. To establish this relationship of trust between the pharmacist and patient, it is appropriate that, during future visits to the service, the same team of people attend the patient.

*Prospecting stage.* The pharmacist must be skilful enough to find out the patient's knowledge about his/her illness and specifically about his/her treatment through a simple conversation, in which the following information is sought: knowledge of the illness, indication and reason for treatment, knowledge of the therapeutic regimen including name of drugs, doses (in units of medication), frequency and other specifications of administration, special storage instructions (if applicable), warnings and adverse effects.

Similarly, the patient's lifestyle, schedule and daily activities must be known in order to be able to establish an individualized program for drug administration.

After the second visit, in addition to acquiring the above data, the pharmacist must estimate the patient's adherence to antiretroviral treatment. As previously mentioned, a single system or method which reliably determines the degree of adherence is difficult to establish, so a combination of systems is recommended. The following are proposed:

- Interviewing the patient.
- Checking attendance at dispensations/programmed visits.
- Counting surplus medication.
- Examining evolution of viral load.

The first system proposed is the interview with the patient. While being attended by the pharmacist, a validated questionnaire may be completed, though a conversation based on indirect questions that give a rough idea of the degree of adherence as described by

**TABLE 5. Recommendations for dispensing**

<b>Pharmaceutical care program</b>
Have a specific area set aside to attend patients
Attend patients on an individual basis and with the maximum confidentiality possible
Establish a system to record and follow up treatment
Set up systems to calculate adherence to treatment
Make individualized information on medication available to patients
Advise the patient on pharmacotherapy
Offer support to help the patient manage his/her medication
Make a name and telephone number available in case the patient needs help (pharmacist from the pharmaceutical service)

the patient him/herself. The questions asked should include the questionnaire in table 4.

Another system easily employed is recording the patient's visits to the pharmacy service to collect medication. The time during which the patient has sufficient supply can be calculated according to the amount of medication supplied. If this period is exceeded, non-compliance should be suspected (with the exception of those specific situations, already discussed).

For the third method, the patient must be told to return the containers, whether empty or only partly full, of all the medication dispensed. This system will make it easy to take a count and calculate adherence. The procedure should be as discrete as possible. If the resources of the pharmacy service do not allow for such a procedure, the patient may be asked to write the surplus units in a diary or on record sheet.

Lastly, viral load can be observed for orientation. Although it cannot be considered an accurate system, as mentioned above, it can warn of lack of adherence or, more importantly, the failure of antiretroviral therapy.

Information obtained from the combined use of all these methods is more valid and accurate than the information any single method alone could provide.

Adherence data must be obtained for each drug, since if for any reason one drug is not being adhered to this can reduce the overall rate of adherence and give an erroneous image of the patient's attitude toward treatment. It is also necessary to record the degree of adherence each time medication is dispensed, since it could vary over time.

In any case, any support measures applied to improve adherence benefit the patient, since supervision itself helps increase adherence.

*Information stage.* This is an extremely important phase within the pharmaceutical care process. Here, the pharmacist must transmit enough knowledge to the patient to achieve correct use of the medication and, therefore, maximum benefit, in order to optimize antiretroviral therapy. Therefore, computer programs and other support tools can be useful in making this job a little easier. Oral information must be combined with written information so that the patient can read about therapy quietly at home, in order to confirm the concepts acquired in the interview. The infor-

mation supplied must be easily understood and use simple language which is easy to follow and include, when possible, pictures in the brochure design<sup>44,53-55</sup>.

To achieve more patient involvement, the individualized treatment sheet should be drawn up together with the patient. This sheet can be obtained from a computer system or from previously available printed material. It must include the necessary information on treatment and treatment planning according to the needs and particular habits of the patient<sup>24</sup>.

The basic information in the brochure should be: name of the drug (preferably the commercial name), dose (expressed pharmaceutically), frequency (indicating whether or not it can be taken with meals), action of the medication, instructions and advice for administration, and most important, any adverse effects or those which are most likely to appear<sup>44</sup>.

The language used during the visit must be appropriate for each patient and non-technical, so the explanations are not difficult to understand. Lastly, the role of adherence must be stressed and encouraged as a determinant of successful therapy and thereby, of the outcome of the disease. This is a process of continuous feedback.

*Dispensing and next appointment stage.* Medication should be dispensed for periods of no more than two months (preferably between 1 and 2 months) coinciding, if possible, with the visit to the doctor to reduce the number of trips to the hospital. The period of dispensation must be adjusted to the characteristics of the patient with regard to adherence, so that, in patients who are poor adherers, the quantity of medication dispensed must be lower to make adherence easier or avoid the waste of medication in patients who probably would not take it.

At the beginning of therapy this period should not exceed 15-30 days, since closer surveillance is necessary, never more than two months, since, as every complier is a potential non-complier as time passes, it is important to reinforce the concept of adherence at each visit to the pharmacist.

The pharmaceutical industry should consider packaging antiretroviral drugs in single-dose packets which are more hygienic, more comfortable for the patient, who does not have to use pillboxes, and favor precise dis-

dispensation of units for a specific period of time. It also allows the patient to avoid loss due to poor storage and reuse of split containers.

At present, such packaging is not available for all antiretrovirals, so the patient should be given, if applicable, special containers that help the patient identify the medication, dose and time of administration. This type of container (daily or weekly) is very useful at the beginning of therapy or on those occasions when a care giver, or the patient him/herself, prepares the medication for a specific period of time ranging from one to several days.

Dispensation records should be computerized for later use of data<sup>56,57</sup>.

Before the patient leaves, both adherence and the return of containers should be stressed. It is important to set the date of the next dispensation, as well as to provide a name and telephone number for consultation on any doubts or questions which come up once the patient has left the hospital.

### **Role of nursing staff**

The task of the nursing staff is mainly patient assistance, and complements the work carried out by the physician. Key points involve informing the patient by resolving any doubts arising during the visit to the doctor and using «counseling» as a working tool to detect possible non-compliance early, through intervention strategies planned with the care team.

A relaxed interview allows the nursing staff to acquire details of the patient's family, personal resources and lifestyle, to analyze the patient's knowledge and degree of awareness of the disease and confidence the patient has in the treatment. Based on this information, a nursing care plan is drawn up, which prioritizes activities and informs the physician of personal or social problems which recommend delaying the initiation of treatment until they are solved.

Furthermore, and when necessary, the nursing staff will select a family member close to the patient to support the patient and act as a positive external reinforcement and reference point. This person will receive a contact number to resolve any doubts and to inform the physician of those situations which require priority attention.

### **Role of the psychological support team**

Psychological support is important for anyone suffering from a chronic disease which

requires continuous care. HIV infection is accompanied by social connotations which, together with the physical connotations, worsen the psychological situation of the patient. These patients may also have other problems, such as substance abuse, sexuality and so on which make it necessary to adopt an individual psychological and social approach and change attitudes and behavior.

Therefore, in order to facilitate suitable care management, a change in attitudes, improved adherence and quality of life, all healthcare professionals, especially physicians, should offer and suggest the suitability of this psychological support both for HIV-infected patients and their friends.

The role of the psychologist/psychiatrist may be very important in certain cases with regard to adherence to treatment, mainly when adherence is poor due to the parallel problems which usually appear in these patients, including depression, anxiety and alcoholism. An early approach to and solution of these situations is essential to achieving good adherence.

Finally, the social and family environment is extremely important in HIV. A positive contribution from this environment will improve adherence. Furthermore, when the patient's own willpower fails, the environment can be motivating. Therefore, friends and family can contribute positively and the care plan should be as easy for them to carry out as possible. It is important that specialists and the care team boost this resource as much as possible.

## **Minimum requirements for the development and implementation of a program of patient care in antiretroviral therapy**

1. Offer a pleasant, comfortable environment for attending patients suitably during the medical visit.
2. Have sufficient medical and nursing staff available.
3. Adapt pharmacy services to attend patients on an individual basis.
4. Pharmaceutical and support staff specialized in the care of HIV patients (psychologists and psychiatrists) should be available.
5. A computer program can provide patients with information on medication.

6. A computer program can record and follow-up on drugs dispensed.
7. Provide support material for patient care.

## Conclusions

Based on all of the above, the following ten recommendations for improving adherence to antiretroviral therapy are made:

1. Given the special characteristics of HIV infection, one of the most important factors in achieving the goals set for antiretroviral treatment is correct adherence. Therefore, no efforts or resources should be spared with regard to programs which favor adherence.
2. Factors influencing adherence depend on the individual, the disease, the therapeutic regimen and the care team.
3. It must be remembered that, exceptionally, prescription of antiretroviral therapy is an emergency and that the patient must be prepared to take on the difficult task of carrying it out correctly. It is necessary to identify and deal with concomitant situations which could impede proper adherence, such as anxiety, depression, alcoholism, drug addiction or social problems.
4. Treatment must be individualized according to the needs and possibilities of each patient. Correct detailed information and the availability of a care team with whom a relationship of trust, flexibility and access is established contribute to achieving treatment objectives.
5. The evaluation of adherence must form part of patient care follow-up. The use of several complementary methods is proposed: evolution of viral load, structured questionnaire and interview, surplus medication count and attendance at dispensation appointments.
6. The evaluation of adherence must be carried out drug by drug and between each dispensation period, in order to solve possible problems.
7. The dispensation period should be no longer than two months. This favors adherence by reinforcing the importance of adherence at each visit to the pharmacy service and, in turn, avoids the waste of medication by patients who do not take advantage of it or who accumulate it due to poor adherence.
8. The care team must be multidisciplinary and maintain an information exchange among its members. This team is comprised of the physicians who prescribe the medication, the pharmacists who dispense the medication and provide pharmacological advice and the nurses, psychologists and psychiatrists as supportive patient-care staff.
9. At all times, the care team must emphasize the importance of adherence, the reasons for adherence and the consequences of incorrect treatment, so they can be corrected employing the measures proposed above.
10. If, in spite of these recommendations, adherence cannot be improved, it may be wise to suspend treatment in some patients.

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