RECOMMENDATIONS OF THE SPANISH AIDS STUDY GROUP (GESIDA), THE SPANISH HOSPITAL PHARMACY SOCIETY (SEFH), AND THE NATIONAL AIDS PLAN (PNS) FOR IMPROVEMENT OF ADHERENCE TO ANTIRETROVIRAL THERAPY
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1. INTRODUCTION

In 1999, the Spanish Hospital Pharmacy Society (SEFH), the AIDS Study Group (GESIDA) as a member of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), and the National AIDS Plan (PNS) first published a series of recommendations for the improvement of adherence to antiretroviral therapy (ART) in adults. These recommendations were updated in 2004.[1,2]

Adherence to treatment continues to receive the attention of health professionals and researchers. Therefore, it seems appropriate to review and update the aforementioned consensus paper in the light of current recommendations on ART.[3]

In the last few years, adherence to ART has been the focus of several publications. In some cases these are action guidelines or reviews,[4,5,6,7] in others, measurement techniques and their reliability are analyzed[8]; the latter are particularly important, as the validity of results depends on how they are analyzed. It seems somewhat pointless to look for reliable but complex methods that can be used in clinical trials but that are of little use in daily clinical practice. Obviously, to measure adherence we must turn to combinations of methods that are easy to use. Combination of methods are necessary, as there is evidence that some are of little use in specific populations.[9]

A good relationship between health professionals and patients makes it easy to obtain appropriate information on adherence and one published meta-analysis examining adherence to medication by patients touches on this topic.[10] Another study evaluates the usefulness of the visual analog scale for measuring adherence to ART.[11]

Several studies analyze the factors that affect adherence and that can be used as indicators or predictors of poor adherence, and thus enable us to identify those patients requiring special attention.[12-15] Logically, one of these factors is the type of treatment, and there is increasing evidence that simplifying therapy can improve adherence.[16,17]

Another relevant aspect is the efficiency (cost-effectiveness) of ART. According to current data from the Multisectorial Plan 2008-2012 of the Spanish Ministry of Health and Consumer Affairs,[18] there are between 120,000 and 150,000 people infected by HIV, although more than 30% may not have been diagnosed yet.

Yearly expenditure on treating a patient with ART can be as high as €9,500 to €10,000. Studies show that between 20% and 50% of patients taking ART are poor adherers.[8-11] Therefore, a national health system must look at adherence to ART as a problem of inefficiency that prevents potential clinical effectiveness from being reached with currently available resources for the treatment of HIV infection.

In any case, we must remember that adherence is not an objective in itself; what is important is the effectiveness of therapy, measured using clinical and biological parameters (viral load and CD4+ T-lymphocyte count). Similarly, the prevention of resistance is also a cause for concern. In this sense, we are more aware that the appearance of resistance and the efficacy of therapy depend on the different drug combinations, even when adherence is similar.[15-17, 19]

Published studies analyzing the results of interventions that attempt to improve the situation[18] have found a direct relationship between adherence to treatment and patient quality of life.[12,20,21] Therefore, interventions must be targeted at improving quality of

life, an objective that can only be reached using a multidisciplinary and tailored approach. In addition to new information on the importance of drug therapy,[22,23] a considerable number of studies examine the role of psychological aspects such as stress or depression.[24-28] We have also seen that some interventions are not useful in certain groups of patients.[25,29]

We can therefore conclude that more and better information is available on adherence to ART. As it is difficult to provide interventions for all patients, we must direct our attention toward those patients who are starting therapy, or who have a history of poor adherence, or who exhibit predictors of poor adherence. Interventions should be multidisciplinary, tailored, and adjusted to new transmission patterns.

The present document has given us the opportunity to review and issue agreed recommendations aimed at improving adherence to ART. Our main objective has been to harmonize criteria and help the professionals responsible for monitoring the health and treatment of these patients (physicians, pharmacists, nurses, psychologists, and social workers).

When preparing recommendations on specific therapeutic interventions, we require in-depth analysis of controlled clinical trials that clearly show the results of specific interventions. However, to carry out this task, it is sometimes necessary to use information from other types of study, such as cohort studies and case-control studies. Therefore, we have followed the levels of recommendation used in the first edition of the Recommendations of the Clinical Advisory Board of the National AIDS Plan. These **levels of recommendation** are based on the origin of the data as follows: **Level A**, controlled and randomized studies; **Level B**, cohort studies and case-control studies; and **Level C**, descriptive studies and expert opinion.

2. DEFINITION OF ADHERENCE

Although there is no universally accepted definition of adherence, we propose the following for HIV-infected patients: “Adherence is the ability of a patient to become appropriately involved in the choice, initiation, and monitoring of ART in such a way as to rigorously fulfill the requirements of treatment with the aim of reaching suitable suppression of viral replication.”

Therefore, incorrect adherence is not only a percentage calculated from missed doses. Adherence in the short and long terms is the result of a complex process that develops over different phases: acceptance of the diagnosis, perception of the need to take treatment correctly, the necessary motivation to do so, willingness and training in the skills to do so, the ability to overcome the barriers and difficulties that arise, and the maintenance of the progress made over time.

Studies carried out with the first highly active antiretroviral drugs showed that maximum efficacy of ART required almost perfect adherence, traditionally more than 95%.[35] Recent studies suggest that lower levels of adherence will still enable patients to reach their therapy objectives with regimens based on non-nucleoside reverse transcriptase inhibitors and protease inhibitors boosted with ritonavir, especially in patients who have achieved undetectable viral loads.[30-33]

3. FACTORS THAT AFFECT ADHERENCE

In recent years, there have been several studies analyzing predictors of adherence. These include longitudinal follow-up studies with several determinations of adherence in different populations (children, adolescents) and in developing countries. However,

the different measurement methods, study populations, and designs make it difficult to generalize about the results.

The factors studied can be divided into 3 main groups: those related to the individual, those related to treatment, and those related to the care team and health system. Table 1 summarizes the different factors involved in adherence to ART.

Table 1. Factors Related to Incorrect Adherence to Antiretroviral Therapy

Patient		**Health Professionals**	**Treatment**
Characteristics	Attitude		
Lack of social or family support.[a] Socioeconomic level. Educational level. Unstable housing. Active drug use.[a] Alcoholism.[a] Depression, psychiatric comorbidity.[a] Health-related quality of life. Knowledge of and beliefs about treatment. Age. Sex. Race. Language.[b]	Mistrust (with regard to the efficacy of the treatment). Hostility (towards health professionals). Shame (social stigma). Fear (adverse effects). Fatalism (pessimism about outcome). Invulnerability. Low perception of self-efficacy.[a] Dissatisfaction with health care and the professional-patient relationship.	Interest in the subject. Professional satisfaction. Communication style (directive / interactive) Attitude (distant / cordial). Accessibility (consultation about doubts or problems). Prejudices. Availability of resources.	Pill burden.[a] Dosing frequency.[a] Duration of treatment.[a] Dietary restrictions.[a] Adverse effects.[a] Intrusion on lifestyle. Type of antiretroviral treatment.

[a] Characteristics that are definitely associated with difficulties in adhering to treatment.
[b] Inability to speak the language is accompanied by other barriers to access to the health system (different health care culture, lack of knowledge about the system).

3.1. Factors Associated With the Individual

Patient characteristics are generally not a good predictor of adherence to treatment. However, some studies have associated adherence with age,[34-38] sex,[39] race,[40,41] cultural level,[34,35,39,41] and economic situation.[35,40]

Other characteristics such as stable housing and social or family support and a good health-related quality of life have shown a more solid association with better adherence.[21,34,36,39,42-47]

According to the study by Carrieri et al, patients born outside the European Union are better adherers than those born inside the European Union. This could be due to the fact that they consider it a privilege to have free access to medication and, therefore, are more motivated to take their treatment.[48]

Psychological factors play a key role in adherence. Anxiety, depression, and stress make it difficult for a patient to adhere correctly to treatment.[34,35,40,41,49,50] Symptoms of depression have been found in more than half of the patients at the beginning of ART. Treatment of depression is associated with greater and better use of antiretroviral drugs, and the association between poor adherence and depression has been related to greater mortality.[48,51,52,53] Given the high prevalence of disease in HIV-infected patients, psychological and psychiatric interventions must be considered an important part of general health care.

Active addiction to drugs and/or alcohol—very common in our setting and potentially treatable[34,36,38,45,49,54-60]—is an important barrier to optimal adherence.

Lastly, the attitude and beliefs of patients about medication, the disease, and the health care team are clearly important factors when accepting treatment and adhering to it correctly.[37,41,45,46,61-64] The patient's ability to understand the relationship between adherence and resistance has also proven to be a predictor of better adherence.[58] If patients are to adhere to their treatment, they must be appropriately informed about their disease and its treatment, they must understand the relationship between risk and benefit, and they must be motivated.

3.2. Disease

HIV infection can develop with or without symptoms, and acceptance of and adherence to treatment can be different in each of these phases. Few studies have taken these factors into account. Studies that evaluate the relationship between CDC stage and adherence have provided contradictory results. Most have found no association,[36,38,41,49,65] although Gao et al[66] found that patients in stage B or C were better adherers than those in stage A, as the former associated poor adherence with an increased risk of complications. Nevertheless, some studies have found a greater degree of discontinuation of HAART in patients with a high viral load (perhaps because they have not achieved virologic control) than patients who have low viral loads.[50,67,68]

We must take into account the perceptions of health care personnel and patients of a condition about which knowledge is constantly changing. In the 1990s, when monotherapy with zidovudine began, patient expectations were high and most studies reflected 60%-80% adherence.[69,70] After 2 or 3 years, the degree of acceptance and adherence fell considerably, to 40%-60%, due mainly to the continuous failures with ART, with the result that expectations fell considerably.[69,70] However, after 1996, the arrival of protease inhibitors and the first combination therapy meant that results were again optimistic and hopeful, expectations improved, and the degree of trust, acceptance, and adherence began to recover slowly.[71] Therefore, some patients who were not good adherers with monotherapy can become good adherers with more complex therapies.

3.3. Treatment

Several studies have shown that adherence decreases when the complexity of treatment increases.[34-36,72-74] In recent years, we have probably obtained the simplest regimens in terms of dosing. Treatment-naïve patients can now take coformulations in regimens of 2-3 daily tablets in 1 or 2 doses with no dietary restrictions. However, no

significant differences in adherence have been found between the administration of drugs in 1 or 2 doses per day, either in patients with HIV or in other chronic conditions.[75]

An important aspect studied in recent years is whether the risk of virologic failure is similar for all regimens when a dose is omitted. Some studies seem to show that with similar levels of adherence, the risk of virologic failure is greater with unboosted protease inhibitors than with boosted protease inhibitors and non-nucleoside reverse transcriptase inhibitors.[19,32,76,77] It has also been suggested that regimens based on non-nucleoside inhibitors have a lower risk of poor adherence than those based on protease inhibitors.[78,79]

Nevertheless, in initial therapy, it has also been shown that there is a linear relationship between adherence and effectiveness when the treatment is based on non-nucleosides—for every 10% increase in adherence, there was a 10% increase in the number of patients who reached sustained undetectable viral loads.[80]

Another aspect to consider, with possible practical implications, is the relationship between adherence and the development of resistance. This relationship is much more complex than the established idea that "nonadherence increases the risk of resistance" and the following differences have been found according to the family of drugs used: in unboosted PI-based regimens, resistance appears even when adherence is good; on the contrary, in NNRTI-based regimens, good adherers rarely experience resistance (it only appears in poor adherers or in patients who take a break from their treatment).[81,82]

Interference with habits, for example in the work timetable or at certain times in the patient's social life, leads some to stop taking their medication or to do so at the wrong time.[83]

Another factor that increases the complexity of treatment are dietary requirements. Some drugs need a very strict dosing schedule because their absorption is highly conditioned by the presence or absence of food when taken. The study by Nieuwkerk et al[84] showed that the percentage of poor adherers increases considerably when diet is taken into consideration.

The onset of adverse effects[36,37,40,45,47,49,54,65,73,79,85-87] is clearly related to adherence. A high number of patients discontinue treatment to avoid the symptoms caused by adverse reactions, regardless of the clinical relevance of this action. In the multicenter APROCO study,[36] patients who complained of a greater number of symptoms with PIs later had poor adherence.

Alterations to body composition are common and can have important psychological repercussions that reduce a patient's quality of life and adherence to ART. Several studies have shown a statistically significant relationship between the perception of the symptoms of lipodystrophy and the failure of adherence.[37,88] This is compounded by the fact that better adherence is associated with a greater risk of lipodystrophy.

The impact of the duration of ART on adherence is controversial. Whereas some authors associate the duration of ART with better adherence, a recent study[89] related reduced adherence to the length of time on treatment, as occurs in other chronic diseases.

3.4. Care Team and Health System

The relationship established between the care team and the patient is extremely important.[66] Trust, continuity, accessibility, flexibility, and confidentiality all have a favorable impact on adherence. The most important factors are probably the provision of detailed and appropriate information adapted to the educational level of the patient and taking decisions together in a framework of mutual trust.[46,90] The results of the study by Schneider et al,[91] who evaluated different aspects of the doctor-patient relationship (general communication style, provision of specific information on HIV infection, participation in decision making, satisfaction and confidence), suggest that the quality of this relationship is an important factor when trying to improve adherence to ART.

Other factors related to the health system, such as accessibility to the center, transport, childcare facilities, and timetables could also have an effect on adherence.[92]

Recommendations

- **The evaluation of possible risk factors to achieve optimal adherence should help in planning specific interventions for each patient. These will generally be multifactorial and multidisciplinary (Level C).**
- **Even if poor adherence seems likely, the patient must have access to treatment and the possibility to take it (Level C).**

4. METHODS OF EVALUATING ADHERENCE

The ideal method of measuring adherence should be highly sensitive and specific, and should enable continuous and quantitative measurements that are reliable, reproducible, applicable in different situations, rapid, and easily affordable.[93]

Methods of evaluating adherence can be classed as direct or indirect.

4.1 Direct Methods

Plasma Concentrations of Antiretroviral Drugs

Although the concentration of drug in plasma is considered the most objective method, many studies show that it has several important limitations. Despite the fact that low levels of drug in have been observed in poor adherers and a good correlation between concentrations and questionnaires has been found,[94,95] there are reports of adequate plasma levels in many patients with self-reported poor adherence.[65,96] Other studies, which consider only this method as the criterion for adherence, did not find significant differences with respect to virologic control.[97-99] However, some authors show that drug level is a variable that independently predicts virologic response,[100] whereas others show an acceptable level of sensitivity but a low specificity for identifying the virologic response.[101]

It is also important to remember that several intraindividual and interindividual variables affect the pharmacokinetic behavior of antiretroviral drugs. Setting a standard threshold to classify patients as good or poor adherers is questionable. Several determinations would be necessary for each patient, as would studies and accurate knowledge of those factors that affect the pharmacokinetic profile of each drug or, at least, the pharmacological group to which it belongs. Although advances are being made in these areas, accurate data are not yet available outside the research environment.[102]

Lastly, it must be pointed out that this method requires expensive and complex techniques; therefore, it cannot be applied in most hospitals. However, clinical criteria could make it useful in specific situations and, given its objectivity, it should be taken into consideration in clinical trials that evaluate the efficacy of new drugs or regimens.

Clinical Outcome and Analytical Data

The clinical outcome and virologic and immunologic results should not be considered methods of estimating adherence, but rather a consequence of adherence. In this sense, adherence studies should systematically consider the relationship between their results and the virologic-immunologic results in a prospective fashion.

Recommendations

- **Direct methods usually have low specificity; therefore, they should not be used individually (Level B). Consider using them only in research.**

- **Clinical outcome should always be analyzed when adherence is studied. It should not be considered a method of calculating adherence, but a consequence of adherence (Level C).**

4.2. Indirect Methods

Evaluation by the Health Professional

Direct and subjective evaluation of adherence by clinicians is common. However, published experiences have shown that health professionals overestimate adherence when direct evaluation is compared with other methods.[103-105]

The main problem of overestimation is that it fails to identify many nonadherers. Thus, the opportunity to treat their behavior and take highly empiric therapeutic approaches is lost.

Recommendation:

- **Health professionals should avoid direct and subjective evaluation. It is known to overestimate adherence and can lead to suboptimal decision making (Level B).**

Electronic Monitoring Systems

Electronic systems that monitor opening of containers (MEMS or eDEM) involve lids containing a microprocessor that records the day and hour the container is opened. These data are processed elsewhere. At present, they are the most objective and reliable method, and show a high correlation with the effectiveness of treatment.[34,106] Thus, some authors have used them as a reference to establish the validity of other methods.[107-110]

Nevertheless, the usefulness of MEMS has been questioned, and not only because of its high cost. These devices can only be used with certain types of container, the patient must be willing to use them, and, sensu stricto, the fact that the container has been opened does not necessarily mean that the medication has been taken. Similarly, the fact that the opening has not been registered does not mean that the dose has not

been taken.[111] In any case, the very fact that the patient accepts the device and the use of a system of continuous monitoring, that is, an intervention, should be considered as a bias when evaluating adherence.

Recommendation:

- **This system is restricted to the field of clinical research. It should be used to evaluate interventions with the aim of improving adherence, and in the evaluation of other methods (Level A).**

Medication Counting

This indirect method involves calculating adherence using the following formula:

$$\% \text{ Adherence} = \frac{\text{No. of units dispensed} - \text{No. of units returned}}{\text{No. of units prescribed}} \times 100$$

This formula has been used successfully in other chronic conditions because of its advantages: it is cheap, it allows a quantitative measure to be made, it is objective, and it is relatively simple. Nevertheless, when this method has been used to calculate adherence to ART, a series of limitations have been observed that make it difficult to use in routine practice.[112] In any case, carrying medication is annoying and uncomfortable, and counting it is difficult for health professionals, as it requires time and personnel.

Furthermore, this system is easily manipulated, even more when patients are asked to collaborate by bringing their surplus medication for counting, or when surprise counts are carried out.

Even though the medication count overestimates adherence when it is compared with MEMS,[113] even when combined with pharmacy service registries,[114] its characteristics have led to its frequent use as a standard.[115,116]

Recommendations:

- **This is an acceptable method, but it should be used in combination with others (Level B).**
- **Its routine use requires time and personnel; therefore, a feasibility study should be carried out before implementation (Level C).**

Dispensation Records

This indirect method parts from the premise that a patient cannot take medication that has not been prescribed to him/her and that he/she takes the medication prescribed correctly. A good correlation with virologic results[99,117] and acceptable sensitivity and specificity have been observed.[65,66] It requires medication to be dispensed centrally. The main limitation is that dispensation does not mean that medication has been taken correctly. Furthermore, patient mobility and sharing medication with friends could bias evaluation.

The tendency is to accumulate medication even though it is not necessary, and this leads to a considerable overestimation of adherence. On the contrary, the use of friends' medication leads to underestimation, although this seems to be less important.

Although the approach is simple, logistic difficulties mean that it is sometimes complex. Adherence can be estimated based on days of delay or number of units of medication dispensed. This can be done globally, or per medication, and there are differences between approaches.

The following simplification can be proposed:

% Adherence = Total no. of medication units dispensed / Total no. of medication units predicted

The formula is calculated using the dates of dispensation and includes the units dispensed from the first date studied until the penultimate dispensation (inclusive). Expected medication use is that which is necessary to fulfill the treatment regimen from the first dispensation to the last.

In the early phases of treatment, periods of approximately 3 months should be studied; in later phases, periods closer to 6 months should be studied.

In Spain, where antiretrovirals are dispensed in national health hospital pharmacies, this system is feasible, relatively cheap, and allows us to establish routine computerized registers with longitudinal follow-up. A good correlation has been observed between adherence measured by this method and virologic outcome.[118]

Recommendations:

- **This method is relatively objective, and the registers are taken on a routine basis, regardless of whether adherence studies are undertaken. In addition, computer software is increasingly sophisticated, thus facilitating the use of these data. Therefore, this method can be recommended as routine practice (Level B).**
- **This method should be combined with others, since the fact that a patient has the medication does not mean that he/she will take it or do so correctly (Level C).**

Questionnaires

Questionnaires involve asking the patient to answer previously defined questions. The answers will be used to evaluate the degree of adherence. This system requires the use of few resources, it is affordable, and it can be adapted to the characteristics of each center.

The main limitation of this method lies in its apparent simplicity. Subjectivity is inherent to questionnaires and, although a correlation has been observed between self-reported adherence and the effectiveness of antiretroviral drugs,[101,106,119] questionnaires have also been shown to have relatively poor sensitivity, which studies show to be very variable when they are compared with more objective methods[114,120] with acceptable specificity. It seems that the correlation with electronic systems is better with questionnaires that calculate adherence over short periods (last 4 days).[121]

Furthermore, there are almost as many questionnaires as published studies. The vast majority have not been validated; therefore, this, coupled with their heterogeneous

nature, means that extreme caution must be used when comparing the results from different populations and using different methods. This was clearly proved in one study where the same population completed different questionnaires, only to give completely disparate results.[122] A greater correlation has been observed with clinical results if the questionnaires are from earlier phases of treatment, if the patient was informed about the confidential nature of the information obtained, and when the adherence threshold was fixed at more than 95%.[123]

The most important validated questionnaire in Spanish is the SMAQ[107] (Table 2).

Table 2. SMAQ QUESTIONNAIRE ON ADHERENCE

1. Have you ever forgotten to take your medication?	□ Yes □ No
2. Do you always take your medication at the prescribed time?	□ Yes □ No
3. Do you ever stop taking your medication if you feel sick?	□ Yes □ No
4. Did you forget to take your medication at the weekend?	□ Yes □ No
5. How many doses have you missed in the last week? [2]	A: None B: 1 - 2 C: 3 - 5 D: 6 - 10 E: more than 10
6. Since your last visit, on how many full days have you not taken your medication?	Days: ….

1. The following sequence is considered nonadherence: 1: yes, 2: no, 3: yes, 4: yes, 5:C, D or E, 6: more than 2 days. The questionnaire is dichotomous—any response indicating nonadherence is considered nonadherent.

2. Question 5 can be used as semiquantitative:
A: 95-100 % adherence
B: 85-94 %
C: 65-84 %
D: 30-64 %
E: < 30 %

However, the questionnaire was validated for patients treated with unboosted protease inhibitors; therefore, it would have to be adapted and validated for the most commonly used regimens today. Another questionnaire, SERAD (Table 3) has been validated for the Spanish population, and provides a quantitative and qualitative evaluation of adherence.[8]

Research into the use of questionnaires to evaluate adherence continues to evolve, and new validated instruments should be incorporated.

Table 3. SERAD QUESTIONNAIRE ON ADHERENCE
Patient Code Date of Evaluation Evaluator

				LAST WEEK					LAST MONTH			
A	B	C	D	E	F	G	H	I	J	K	L	M
Time	Medication	No. of tablets		No. of times patient did not take dose	Total no. of tablets not consumed per dose	Reasons for not taking dose (eg, a3, b1)	No. of times patient does not adhere to dosing conditions	Reasons for not adhering to dosing conditions	No. of times patient did not take dose	Total no. of tablets not consumed per dose	Reasons for not taking dose (eg, 3a, 1f)	No. of times patient does not adhere to dosing conditions
	Breakfast											
	Lunch											
	Dinner											

a) Not having medication at the time of dosing
b) Just forgot
c) Trying to avoid side effects
d) Fell asleep
e) Was doing other things that were not compatible with taking medication
f) Didn't want people I was with to see me taking medication
g) Changes in daily routine (public holiday, weekend, vacation, etc)
h) Was sick
i) Too many tablets
j) Felt depressed or demotivated
k) Ran out of tablets
l) Didn't want to take or didn't feel like taking medication
m) Prescribed by doctor
n) Did not understand doctor's prescription correctly
o) Other

Apart from this last month, how many times do you remember not taking your medication since the last visit?

None
1 or 2 times
3 to 5 times
6 to 10 times
11 or more times
Reasons for not taking medication

Recommendations:

- **These methods are simple and inexpensive, and are particularly useful if the patient is identified as a poor adherer. In research, questionnaires and the results they yield should be compared taking into account the following 3 attributes: adherence evaluated as a qualitative variable of behavior, the classification of adherence as a continuous and dichotomous variable, and the time interval evaluated (Level A).**
- **Questionnaires can be recommended, in combination with others, as long as they have been previously validated and adapted to the specific context of application (Level A).**

Combinations of Methods

In general, questionnaires, medication counts, and pharmacy dispensation records overestimate adherence.[114,116] MEMS-type systems probably underestimate adherence.[116]

Although notable advances have been made in characterizing the specificity and sensitivity of the different methods, in their validation, and in the analysis of their limitations and interrelationships, the recommendation to combine several methods should remain in force so that accurate information can be obtained about the real situation.[1,124]

Recommendations:

- **An acceptable minimum approach would involve a 3-monthly validated questionnaire and dispensation register (Level B).**
- **In the context of a clinical trial that might even include interventions aimed at improving adherence, at least one of the following more objective methods should be used: MEMS, determination of drug plasma concentrations, and medication counts (Level C).**

5. STRATEGIES FOR IMPROVING ADHERENCE TO ANTIRETROVIRAL THERAPY

There are basically 3 strategies aimed at improving antiretroviral therapy:

- Help and support strategies
- Intervention strategies
- Strategies involving the therapeutic regimen

5.1. Help and Support Strategies

Help and support strategies should be centered on the patient, regardless of his/her level of adherence, and should involve health education, communication, and psychosocial support. Each hospital should adapt strategies to its own situation (caseload, human resources, support services).

In support strategies, teamwork is essential and must involve all those who care for the HIV-infected patient: physicians, pharmacists, nursing staff, and, where possible, psychologists and psychiatrists. Coordination with primary health care, social services, and nongovernmental organizations is a desirable objective in the global care of the HIV-infected patient.

In the case of patients who are not from Spain, integration in HIV-related planning will involve the development of culturally and linguistically adapted strategies including peer counseling, intercultural mediation, and translation.

5.1.1. Prescription and Follow-up of ART

- **Role of the Physician**

Before prescribing medication, the physician should remember some basic premises: the best opportunity to achieve effective therapy is during the first treatment regimen. Furthermore, on rare occasions, ART should only be started quickly as an emergency measure in cases of postexposure prophylaxis and prophylaxis of vertical transmission during labor.

In asymptomatic patients with a relatively conserved immunological status, initiation of ART can be delayed for a few months until any underlying condition (alcoholism, depression, drug addiction) is resolved with the help of the appropriate service or professionals. The importance of starting therapy will be explained during subsequent visits. The symptomatic patient, however, must be prepared more quickly. If the patient accepts treatment, comorbid conditions can be treated when treatment starts.

Once the decision to start ART has been taken, prescription involves 3 different phases: information, agreement and commitment, and finally maintenance and support. The characteristics of these phases are summarized in Table 4.

Table 4. RECOMMENDATIONS FOR PRESCRIPTION

PHASE	OBJECTIVES
Informative	Identify possible risk factors for adherence Ascertain the social, work, and family situation Know the psychological situation and the concomitant condition (drug dependence, alcoholism) Explain the objectives, dosing regimens, and potential adverse effects of treatment Offer possible alternative treatments Highlight the importance of adherence for the efficacy of treatment
Agreement and commitment	Adapt treatment to the patient's daily routine Agree on regimens and doses with the patient Postpone treatment until agreement and commitment have been made Treat concomitant conditions (depression, anxiety, alcoholism, drug dependence) Ask the patient to make a commitment to adhere to treatment
Maintenance and support	Evaluate adherence to treatment

	Determine problems and offer solutions Accessible health care (telephone, day hospital, outpatients' clinic)

5.1.2. Follow-up of ART

- **Role of the Pharmacist**

When the drug has been prescribed and dispensed, the pharmacy service can become involved with the patient and carry out the activities that make up pharmaceutical health care. Pharmacotherapeutic follow-up is the professional activity through which the pharmacist takes charge of the patient's medication needs by continuously and systematically detecting, preventing, and solving medication-related problems. Records are kept, and the service collaborates with the patient and with health care professionals. Table 5 summarizes the objectives of pharmaceutical care.

Table 5. PHARMACEUTICAL CARE PROGRAM

PHASE	OBJECTIVES
Presentation	Presentation Explain the procedure the patient must follow for subsequent dispensations.
Prospecting	Determine the patient's level of knowledge about his/her disease, and the indication and reason for treatment. Determine the level of knowledge about the therapeutic regimen, including drug names, doses (in medication units), frequency, and aspects related to administration, special conditions of conservation, precautions, and adverse effects. Determine the patient's lifestyle, timetables, and daily activities in order to be able to set up an individual schedule for the administration of the drugs. Determine which drugs the patient is taking (other than ART) and detect possible interactions. Evaluate adherence.
Information	Give the patient enough information to take the medication correctly ART is optimized and the maximum benefit obtained. Provide oral and written information on treatment and planning of treatment according to the needs and particular habits of the patient. Basic information should include the name of the drug (preferably the commercial name), dose (expressed in its pharmaceutical form), frequency (and whether it is to be taken with meals or not), action of the medication, considerations and advice about administration, and the main adverse effects or those that are most likely to appear. Stress the importance of adherence.
Dispensation and appointment for the next	Dispensation. Set the date for the next dispensation. Provide a name and telephone number for consultation and resolution of

visit	doubts the patient might have once outside the hospital.

The amount of each medication dispensed must be adapted to the characteristics of the patient in terms of adherence; thus, poor adherers must receive smaller amounts to make it easier to take and prevent waste. At the beginning of therapy, this period must be no longer than 15-30 days, since supervision must be closer. Depending on the patient's degree of adherence, or any problems with adherence the patient mentions, dispensation can coincide with clinical checkups in order to avoid unnecessary trips.

The patient can be given containers that help identify the medication, dose, and time of administration. This type of device (daily or weekly) is very useful at the beginning of therapy or on those occasions when a carer, or the patient, prepares the medication for a given period of time, which may range from 1 to several days.

Dispensation should be recorded on computer by the pharmacy service. This will make it easy to use data and enable indirect adherence reports to be prepared (by analyzing the medication dispensed). As indicated above, routine evaluation of adherence during ART is a key factor for decision-making, and these evaluation reports should be provided to the physician as a diagnostic tool.

- **Role of Nursing Staff**

Nurses play an essential role, with full-time dedication to the integrated care of the HIV-infected patient. There must be a relationship of trust, accessibility, confidentiality, and flexibility at all times between the care team and the patient.

The nurse's role involves supporting the patient, and the key areas involve informing the patient by clarifying doubts arising from medical visits and using counseling as a work tool. The nurse must also identify possible nonadherers early and help the care team design intervention strategies.

Similarly, the nurse will learn as much as possible about the patient's habits and personal and family resources, and will analyze the patient's knowledge about the disease and the degree of awareness and trust the patient has in order to start treatment. This information will enable a nursing care plan to be established, and priorities to be set. The nurse will inform the physician of any personal or social problems that should be solved before treatment is started.

Once it has been decided to start treatment, an analysis must be made of the general characteristics of a typical day so that treatment can be adapted to the patient's lifestyle by means of a medication schedule. This schedule should be set out in writing.

Before bringing an interview to an end, the nurse must ensure that the patient has understood the explanations and clear up any doubts. At this point, close external support (eg, family, partner) must be chosen to support the patient. This person must be given a contact number in case doubts should arise and so that the physician can be informed about situations that might require priority attention.

- **Role of the Psychologist and/or Psychiatrist**

In many cases, poor adherence can be caused by emotional problems that are directly or indirectly linked to the disease itself. As HIV infection is asymptomatic for long periods, some HIV-infected patients show little perception of their condition as such, and this could result in insufficient or incorrect care of their health.

The psychologist can help the patient to adapt correctly to the disease in the various situations that arise from diagnosis to the start of antiretroviral therapy, and to deal with the different changes that occur. The management of adverse effects and their repercussions for emotional status and quality of life, and the patient's relationship with his/her family and social context are areas where the psychologist can help. Correct adaptation to the disease and suitable awareness of it will undoubtedly lead to better overall health care, which includes taking medication naturally. The psychologist can also help in cases of anxiety and depression, which are common not only in recently diagnosed patients, but also in those who have been in treatment for some time and who, logically, are tired and dejected. Very often, forgetting to take medication or intolerance to drugs reflects depressive emotional states that must be uncovered and tackled by the psychologist.

The main role of the psychiatrist is to prescribe medication when a psychiatric condition is diagnosed that is associated or not with HIV infection. Psychiatric patients who are not carefully monitored will not be able to obtain the necessary degree of adherence to treatment.

The family and social setting are also extremely important in solving problems related to HIV. A positive approach from this area will boost adherence. If possible, an attempt should be made to involve people who are emotionally important for the patient.

Recommendations:

- **Before starting ART, the patient should be prepared and any possible limits to adherence should be identified and corrected. If the patient's clinical situation allows, the possibility of delaying treatment should be evaluated (Level C).**
- **Any patient who starts or changes ART should be offered an education program. This will be carried out by health professionals with experience in the management of HIV infection, exhaustive knowledge of ART, and communication skills, so that the patient can have a verbal and written version of the information and instructions on the medication that makes up ART (Level C).**
- **Every effort should be made so that the care team (physicians, pharmacists, nurses, psychologists, and psychiatrists) are available to resolve any doubts and problems the patient may have during treatment (Level C).**

5.2. Intervention Strategies

No intervention is better than others for improving adherence to any pharmacological treatment, and it seems clear that interventions that combine cognitive, behavioral, and emotional components are more efficacious than those focusing on only one of these areas.[125] Table 6 summarizes the potential causes of poor adherence and the possible interventions.

Table 6. CAUSES OF POOR ADHERENCE AND POSSIBLE INTERVENTION STRATEGIES

	Potential causes of nonadherence	Possible interventions
Socio-economic and educational factors	Lack of social and/or family support. Few resources. Low educational level.	Look for alliances with family and friends. Ascertain social needs. Involve community organizations. Intensive education, with clear explanations that are understandable and adapted.
Factors involving the care team	Lack of resources. Impersonal care being given to large numbers of patients. Lack of coordination between the different care support services. Insufficient training in ART. Lack of accessibility. Deficient training in the professional-patient relationship.	Accessibility to continuous care. Multidisciplinary team. Adequate and coordinated material and human resources. Solid grounding in ART and patient care. Consider directly observed therapy in specific care settings.
Treatment-related factors	Adverse effects, size and palatability of the medication units, number of daily doses. Interference in the patient's life. Lack of adaptation to the patient's needs and preferences.	Simplify the regimen. Tailor treatment. Comorbidity, preferences, interactions. Special techniques for taking medication. Help to develop reaction mechanisms (eg, anticipate and manage adverse effects).
Patient-related factors	Nonacceptance. Rejection of the diagnosis. Rejection of the treatment (beliefs and attitudes) Forgetfulness and barriers. Inadequate comprehension of the disease and its treatment. Inadequate understanding of the risk-benefit ratio. Reasons for dosing and adherence. Comorbid psychiatric conditions. Use and abuse of drugs.	Analyze the patient-professional relationship. Negotiate and agree on a therapeutic plan. Encourage the perception of indicators of the need for treatment. Inform about the risks and benefits of treatment. Associate doses with daily activities. Special techniques and help with adherence (medication diaries, alarms, telephones, etc). Improve communication between the patient and the professional. Information on the disease and its treatment, reason for dosing, risks involved with nonadherence. Oral and written information. Check understanding. Refer for psychological intervention in dysfunctional areas or psychiatric intervention if psychiatric conditions are detected.

The best levels of evidence are based on randomized and controlled studies. The best intervention is that based on informing and educating the patient in order to reach the highest degree of consensus and commitment and make the patient see the objective of the treatment and the reasons for adherence.[94,126,127-131] Some randomized studies show that some interventions improve adherence, without achieving changes in virologic control.[132] Another randomized study observed that telephone reminders improved adherence, although the improvement was not significant in adherence or virologic outcome.[133] A meta-analysis that evaluated behavioral intervention strategies

to improve adherence in 19 studies with 1839 patients showed that adherence improved in the intervention groups and that the number of patients with undetectable viral load tended to decrease.[134]

The most efficacious intervention has probably been structured interpersonal support for adherence, in which specially trained personnel use tailored strategies to improve adherence. In this randomized study including 928 patients, not only was there an improvement in adherence, but there was also an improvement in immunologic and virologic outcome in the intervention group.[135]

Directly observed treatment is another strategy used to improve adherence. It has been used successfully to treat tuberculosis and attempts have been made to adapt it to the characteristics of ART. Several studies have provided favorable preliminary results of this approach in the short and long term. Most have been carried out in methadone maintenance programs or in prisons.[136-139]

For other patients, the programs that adapt best to ART have not been well defined. Furthermore, it is necessary to clarify the optimal duration of ART, determine the best candidates for these programs, and decide whether the programs are cost-effective.

As for evaluation of specific interventions to improve adherence, it is necessary to consider methodological questions, mainly those involving the type of intervention in the control group, given that the recommendations for improving this aspect of treatment are, to a greater or lesser extent, part of the treatment of the HIV-infected patient in usual clinical practice.

Recommendations:

- **Tailored intervention strategies based on psychoeducational approaches and personal advice and that can adapt ART to the patient's lifestyle and help solve problems have proven efficacious for increasing adherence and improving the response to treatment (Level A).**
- **These strategies should be implemented in health centers by a mix of professionals who care for HIV-infected patients (Level C).**
- **Directly observed treatment cannot be generally recommended. However, it could be of interest and effective in specific groups (prisoners, severely marginalized persons, methadone maintenance programs) (Level C).**

5.3. Strategies Involving the Therapeutic Regimen

Recent advances in ART have made possible highly potent and simple treatments that play an important role in favoring adherence. These advances are the coformulation of several active ingredients in a single dose, the availability of drugs that can be administered once daily, and, therefore, the possibility of combinations that can be taken in a single daily dose (QD).

Once-daily regimens have created a great deal of interest. Nevertheless, other questions must be resolved conclusively. These include interactions, toxicity, effectiveness, relationship with adherence, and impact on quality of life. It must be remembered that the use of once-daily regimens is one of the many possible interventions, and its impact depends both on individual factors and on external factors, including pill burden, tolerance, potency, efficacy, and resistance.

Furthermore, simplification of ART is defined as a change in a regimen with which a suitable response has been obtained for another that maintains the same efficacy while allowing its complexity to be reduced. Simplification strategies are widely reviewed in the recent consensus document from GESIDA/PNS on antiretroviral therapy in adults.[3]

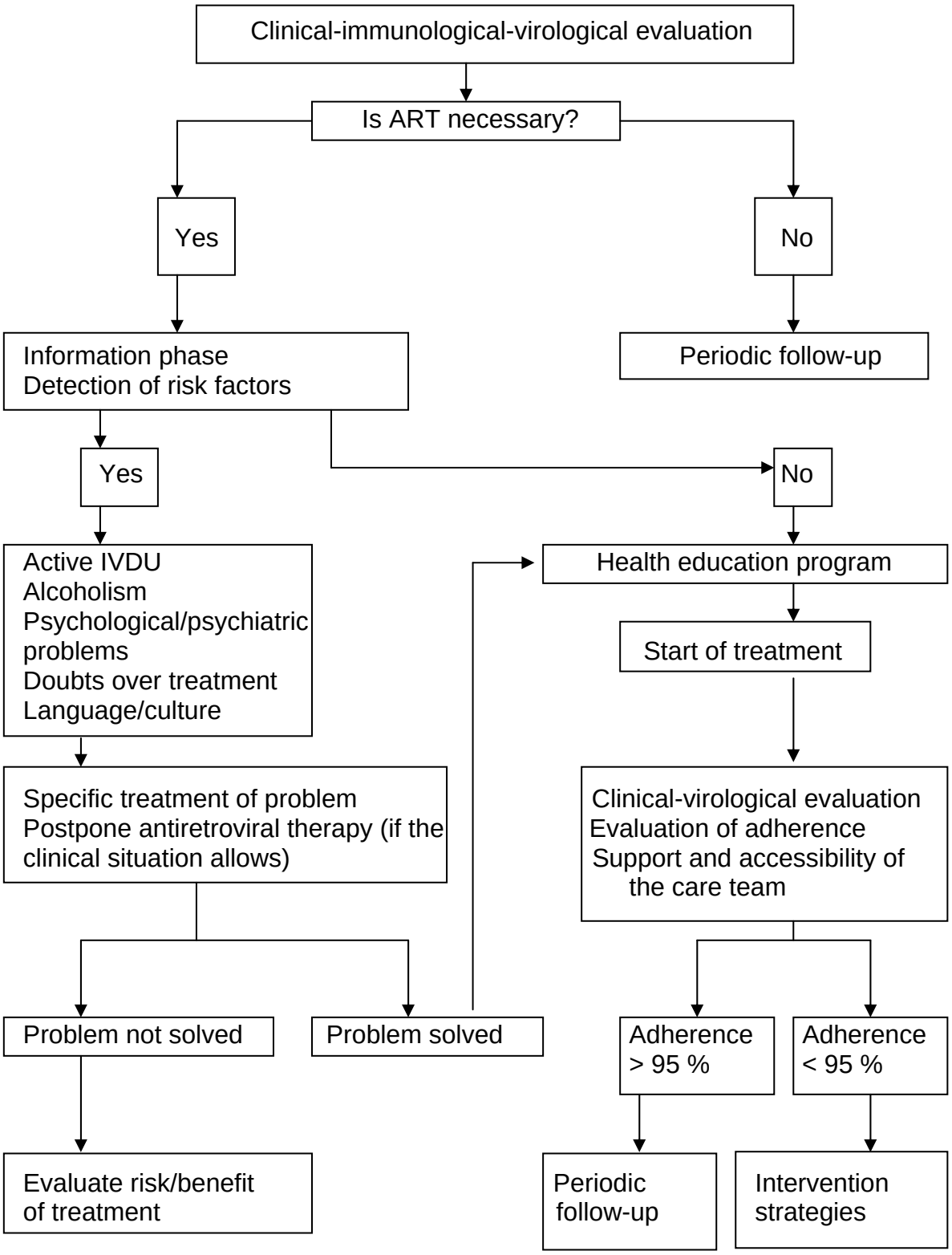
Recommendations:

- **ART should be tailored and adapted to the needs and preferences of the patient. Simpler regimens with a lower number of daily doses and a lower pill burden are advisable (Level C).**
- **In the case of patients with maintained virologic suppression achieved using a complex regimen, ART could be simplified to regimens that have shown similar or better safety and efficacy (Level A).**

6. CONCLUSIONS

Figure 1 shows a decision-making algorithm that attempts to summarize the recommendations developed above.

Figure I. Algorithm for starting and maintaining antiretroviral therapy



1. Adherence plays an essential role in the decision to initiate ART and in the duration of the virologic response. Lack of adherence has been shown to be the principal cause

of therapeutic failure and is positively correlated with an increase in hospital admissions, progress to AIDS, and mortality of HIV-infected patients. Given its high cost, it is also an inefficient use of public resources.

2. The most important factors associated with adherence include the complexity of treatment, side effects, psychological problems, active drug and/or alcohol addiction, the lack of social and family support, and the patients' attitudes to and beliefs about treatment.

3. A combination of several methods should be used to estimate adherence. Routine follow-up should involve feasible methods that are adapted to the real situation of the hospital and universally applicable. The acceptable minimum would involve the combination of a validated questionnaire and the hospital pharmacy dispensing register.

4. Any patient starting or switching ART should undergo a health education program on treatment with experienced health professionals who know how to manage individuals infected by HIV. The care team (physicians, pharmacists, and nurses) should try to be as available as possible to resolve the patient's doubts and problems during treatment.

5. In the case of patients who do not reach acceptable levels of adherence, intervention strategies should be applied. These should be multidisciplinary, and have a tailored, psychoeducational approach to adapt the ART regimen to the patient's lifestyle and provide problem-solving strategies. If psychological problems or psychiatric disorders are detected, the interventions should go further than being educational—they should attempt to improve the patient's emotional status and should be carried out by mental health professionals (psychologists and psychiatrists).

6. Regimens with a lower pill burden are acceptable. ART can be simplified to regimens that have shown similar or better efficacy and safety.

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