OBJECTIVE. This consensus document is an update of antiretroviral therapy (ART) recommendations for adult patients infected with the human immunodeficiency virus (HIV-1).

METHODS. To formulate these recommendations, a panel composed of members of the Grupo de Estudio de Sida (GESIDA; AIDS Study Group) and the Plan Nacional sobre el Sida (PNS; Spanish AIDS Plan) reviewed the advances in the current understanding of the pathophysiology of HIV, the safety and efficacy findings from clinical trials, and the results from cohort and pharmacokinetic studies published in biomedical journals or presented at scientific meetings over the last years. Three levels of evidence were defined according to the source of the data: randomized studies (level A), cohort or case-control studies (level B), and expert opinion (level C). The decision to recommend, consider or not recommend ART was established in each situation.

RESULTS. Currently, the treatment of choice for chronic HIV infection is the combination of three drugs of two different classes, including 2 nucleosides or nucleotide analogs (NRTI) plus 1 non-nucleoside (NNRTI) or 1 boosted protease inhibitor (PI/r). Initiation of ART is recommended in patients with symptomatic HIV infection. In asymptomatic patients, initiation of ART is recommended on the basis of CD4+ lymphocyte counts and plasma viral load, as follows: 1) therapy should be started in patients with CD4+ counts of < 200 cells/µL; 2) therapy should be started in most patients with CD4+ counts of 200-350 cells/µL, although it can be delayed when CD4+ count persists at around 350 cells/µL and viral load is low; and 3) initiation of therapy can be delayed in patients with CD4+ counts of > 350 cells/µL. The initial objective of ART is to achieve an undetectable viral load. Adherence to therapy plays an essential role in maintaining the antiviral response. Therapeutic options are limited with the development of cross resistance and ART failure. Genotype studies are useful in these cases. More information regarding the studies analyzed and the panel recommendations for adherence, toxicity, treatment during pregnancy, patients with hepatitis B or C virus co-infection, and post-exposure prophylaxis can be accessed at www.gesida.seimc.org.

CONCLUSIONS. CD4+ lymphocyte count is the most important reference factor for initiating ART in asymptomatic patients. The large number of available drugs, the increased sensitivity of tests to monitor viral load, and the ability to determine viral resistance is leading to a more individualized approach to therapy.

Key words: Antiretroviral treatment. AIDS. HIV infection. GESIDA. PNS (Plan Nacional sobre el Sida). Antiretroviral resistance. Guidelines.
elección de la infección crónica por el VIH-1. Estas pautas deben incluir 2 análogos de nucleósido o nucleótido (AN) + 1 no análogo (NN) o 2 AN + 1 inhibidor de la proteasa (IP) potenciado con ritonavir. En los pacientes con infección por VIH-1 sintomática se recomienda iniciar el TARV. En los pacientes asintomáticos el inicio de TARV se basará en la cifra de linfocitos CD4+ /µL y en la carga viral plasmática (CVP). 1) en pacientes con linfocitos CD4+ < 200 células/µL se recomienda iniciar el TARV; 2) en pacientes con linfocitos CD4+ entre 200 y 350 células/µL en la mayoría de los casos se debe recomendar el tratamiento, si bien se podría diferir cuando la cifra de linfocitos CD4+ se mantiene próxima a 350 células/µL y la CVP es baja. 3) en los pacientes con linfocitos CD4+ > 350 células/µL se puede diferir el inicio del TARV. El objetivo del TARV es lograr una carga viral plasmática indetectable. Las opciones terapéuticas en los fracasos del TARV se ven limitadas por la aparición de resistencias cruzadas. Los estudios genotípicos en estos casos son de utilidad. Se puede encontrar más información sobre los estudios analizados, las recomendaciones del panel sobre adherencia, toxicidad, tratamiento de la embarazada, pacientes coinfectados por VHB o VHC o sobre la profilaxis postexposición en la página web www.gesida.seimc.org. Conclusiónes. La cifra de linfocitos CD4+ es el factor de referencia más importante para iniciar el TARV en pacientes asintomáticos. Por otra parte, el número considerable de fármacos disponibles, los métodos más sensibles de monitorización de la CVP y la posibilidad de determinar las resistencias hacen que las estrategias terapéuticas deban ser cada vez más, mucho más individualizadas.


Introduction

Since highly active antiretroviral therapy became part of clinical practice in 1996, the number of antiretroviral drugs available and their possible combinations have continued to grow. At the same time, research in the field of antiretroviral therapy (ART) has taught us the best way of using these combinations, although clinical decisions on the best antiretroviral therapy should be based on expert recommendations in the absence of data of better methodological quality. This situation has led different international scientific societies and institutions to prepare and update their own recommendations on the use of antiretroviral drugs1-3.

In Spain, the Plan Nacional sobre el Sida (PNS: Spanish AIDS Plan) and the Grupo de Estudio de Sida (GESIDA: AIDS Study Group) of the Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC: Spanish Society for Infectious Diseases and Clinical Microbiology) have been working together closely for several years to obtain a consensus among the health-care professionals who treat HIV-1-infected individuals, and provide updated and validated recommendations to physicians with less experience in the treatment of this infection. Therefore, they regularly publish documents that update recommendations on antiretroviral therapy in HIV-1-infected adults. These documents are drawn up by an expert committee selected by both institutions. The present document replaces that published in 2004 and its 2005 update published on the web pages of GESIDA and the PNS. These guidelines have been updated by reviewing the most relevant scientific data taken from scientific journals or communications at scientific meetings. This document aims to answer questions relating to the indication to initiate or modify ART, and the selection of the most suitable combinations. The committee has also performed an in-depth review of other aspects associated with antiretroviral therapy, such as adherence, toxicity, drug-drug interactions, or special situations (coinfection with hepatitis virus, therapy in pregnant women, or post-exposure prophylaxis). However, for editorial reasons, these special areas are not dealt with in the present article although they are available in an extended version of the document available on the web pages of GESIDA (www.gesida.seimc.org) and the PNS (http://www.msc.es). The extended version also provides a more exhaustive review of the studies and data on which the recommendations are based. The characteristics of the different antiretrovirals, their possible pharmacokinetic and adverse effects, and the cost of the recommended regimens are presented in a table.

Data on antiretroviral therapy change constantly; therefore, readers should regularly consult other sources of information.

Evaluation of the degree of scientific evidence

As in previous editions of this document, the levels of recommendation used in the first edition of the Recommendations of the Advisory Committee of the National AIDS Plan, which are based on the source of the data: level A: randomized and controlled studies, level B: cohort or case-control studies and level C: descriptive studies or expert opinion.

General principles

The state of the art in HIV-1 infection allows us to establish the following principles:

1. ART of choice is based on combinations of three drugs, as this delays clinical progression, reduces hospital admissions and infection-related costs, and significantly increases survival1-14.
2. Adherence to ART plays a crucial role in virological response and its duration12.
3. Clinical symptoms, CD4+ lymphocyte count and HIV-1 RNA viral load (VL) are the basis for taking therapeutic decisions in different clinical situations and for monitoring the effectiveness of ART1-3,15.
4. Treatment aims to reduce VL to below the limits of detection set by commercially available methods, wherever possible by ultra-sensitive methods (< 20 to < 50 copies/mL), and for as long as possible1,3,6-17.
5. Resistance is an inevitable phenomenon when HIV-1 is exposed to the selective pressure of one or more drugs that do not manage to suppress viral replication.

6. In patients with advanced immunodepression, restoration of the immune system in both quantitative terms (absolute CD4+ lymphocyte figure) and qualitative terms (quality of the immune function) is possible with current ART regimens.\(^{(16,17)}\)

7. As of January 2007, we have at our disposal 20 drugs belonging to four families which, together with other tools for guiding ART, make possible therapeutic strategies that are much more dynamic and individualized.

8. Medium-term and long-term toxicity of antiretroviral drugs is a limiting factor that forces us to seek out new options capable of limiting or eliminating side effects while maintaining antiviral potency.\(^{(19)}\)

9. There are probably several ART regimens that are similar in terms of antiretroviral potency,\(^{(2,3,34)}\) and choice will depend on patient and physician preference, secondary effects, tolerance and adherence, previous therapy, possible cross-resistance, potential pharmacological interactions, and cost and availability of antiretroviral drugs.

10. The increasing complexity of ART means that patients must be attended by specialized staff with sufficient knowledge and means.\(^{(19)}\)

11. Prevention of HIV-1 infection is a basic aspect of HIV-1 infection that must never be forgotten in clinical practice.

### Parameters for guiding antiretroviral therapy

The patient's clinical situation (presence or absence of opportunistic events), CD4+ lymphocyte count, and VL are the parameters used to take decisions on initiating and modifying ART and to monitor its efficacy.

#### Clinical manifestations

Most opportunistic events occur in immunodepressed patients whose criteria indicate that ART should be initiated. The onset of an opportunistic disease in a patient on ART should be considered as a therapeutic failure. Nevertheless, the onset of an opportunistic infection during the first 3-6 months of ART in patients with advanced immunodepression and a suitable virological response (immune reconstitution) cannot be considered a therapeutic failure.\(^{(22,23)}\)

**Recommendations**

- Clinical progress must be monitored at all visits, since it could be a reason for switching therapy (level C).
- In the care setting, a clinical check-up should be made 4 weeks after initiating ART and then every 3-4 months. In patients with advanced immunodepression, a more frequent follow-up should be performed, at least initially, whereas in stable patients this period can be extended (level C).
- Biological check-ups (VL, CD4+ lymphocytes) should be carried out with the same frequency as the clinical check-ups (every 3 or 4 months). It is very important to evaluate the adherence, toxicity, and potential pharmacokinetic interactions of ART at all check-ups.

### CD4+ lymphocytes

One objective of ART is immune restoration, and the most practical way to evaluate it is by measuring the increase in the number of CD4 lymphocytes that can be observed during the first weeks after initiating ART.\(^{(24-26)}\)

The proliferative response to memory antigens and mitogens is restored and this allows prophylaxis of opportunistic infections to be suspended.\(^{(26)}\)

The increase in the number of CD4 lymphocytes is slow but constant over time. There are no data that enable us to provide a definition of adequate immune response. In conventional techniques, cell kinetics studies show that during the first year there should be an increase of at least 50-100 CD4 lymphocytes/µL. Immune failure is usually preceded by virological failure and modifications to ART usually depend on VL. Discordance between the immune response and the virological response to ART can sometimes be observed.

**Recommendations**

- The number of CD4 lymphocytes is the most important parameter for deciding when to initiate ART. Therefore, it should be measured at the first visit so that decisions on when to initiate ART can be made (level B).
- On the contrary, the number of CD4 lymphocytes is a less important criterion than VL when deciding on modifications to therapy.
- In asymptomatic patients, the number of CD4 lymphocytes should be measured every 3 or 4 months; this interval can be extended if the patient is stable. The variability of the technique (± 20%) means that the number of CD4 lymphocytes must always be measured before taking any decisions concerning therapy.\(^{(26-28)}\)

### HIV-1 viral load in plasma

The objective of ART is to suppress viral replication as quickly and for as long as possible. VL falls quickly (1-2 log/mL) after initiating ART and the nadir reached at 4-8 weeks correlates with the duration of the response.\(^{(31-33)}\)

In naive patients, VL levels that are undetectable using conventional techniques (< 200/50 copies/mL) are usually reached after 3-8 weeks of ART.\(^{(34)}\) Some patients, especially those who start with a high VL, can take more than 24 weeks to reach levels below 20-50 copies/mL.\(^{(35)}\)

It is important to reach a VL below 20-50 copies/mL, since it has been shown that, although the virus replicates in lymphatic tissue, if VL is below this level, resistance mutations are not selected.\(^{(35,37)}\) Furthermore, the duration of the virological response at 18-24 months is much greater for those individuals who reach a VL of < 20 copies/mL than for those who maintain a VL of between 20 and 500 copies/mL.\(^{(35)}\) Although some studies show that there is a greater risk of failure in patients who experience frequent transitory rebounds in VL (blips), most do not show a great incidence of virological failure in patients with a complete virological response.\(^{(35,38)}\) In any case, a VL above 50 copies/mL in two successive determinations must be considered a virological failure.

**On the basis of viral kinetics in patients with ART, the criteria for virological response and failure are as follows:**

Virological response: VL < 20/50 copies/mL at 16-24 weeks.

These patients have a virological response at 1 month (de-
crease $>1 \log_{10}$/mL, and at 3-4 months they have an undetectable VL using conventional techniques.

Virological failure: any of the following situations define virological failure: a) detectable VL at 24 months after initiating ART, or b) after reaching an undetectable VL ($<50$ copies/mL), it becomes detectable in two successive determinations.

**Recommendations**

- VL is the main parameter for evaluating the efficacy of ART, for defining its failure and, therefore, for taking decisions about modifications to therapy (see “Experienced patients”). At present, VL is recognized as a secondary criterion for the initiation of ART, complementary to the number of CD4 lymphocytes. Follow-up of the efficacy of ART should use, whenever possible, an ultrasensitive method of measuring VL (level B). The same technique should be used habitually. VL should always be confirmed with a second determination before making any decisions about therapy (level B).

- As far as frequency of tests is concerned, it is advisable to measure VL four weeks after initiating ART in order to verify whether there is a virological response and as an indirect measure of adherence. Levels should be measured every 3-4 months afterwards, although this interval can be extended in stable patients. We must bear in mind that, if VL is measured after an intercurrent viral process or after vaccination (e.g., anti-influenza or hepatitis B vaccine), there may be transitory rebounds in VL. In this case, a new analysis is recommended after a few weeks.

### Resistance of HIV-1 to antiretroviral drugs

The appearance of viral strains with resistance variants can be detected using genotypic or phenotypic techniques. Genotypic techniques detect specific changes in the genomes of the enzymes that are targeted by the action of drugs (reverse transcriptase and protease), whereas phenotypic techniques determine the response of most of the viral population at increasing quantities of the different drugs. Both techniques have limitations: on the one hand, the resistant variants may not be detected by most genotypic and phenotypic tests until they make up 20% of the viral population and, on the other, technical limitations make it difficult to obtain reliable results when VL is below 1,000 copies/mL of HIV-1 RNA. Finally, resistance tests should be performed during ART and not after interrupting it, since the resistant viral population will be replaced by a sensitive population a few weeks after the drugs are withdrawn. The results of resistance tests should be interpreted bearing in mind previous ART and resistance studies, as well as adherence.

The literature contains numerous studies from the developed world that have analyzed the frequency of primary resistance in patients with acute and chronic HIV-1 infection before receiving ART. We now know that most mutations can be detected over many years and that, as has recently been confirmed in the U.S. and in Europe, the prevalence of primary resistance has increased considerably, in some cases to more than 10%. Nevertheless, in order to know the possible implications for therapy in a specific country, it is very important to analyze local data. Several studies have been carried out in both situations in Spain

### Acute HIV-1 infection

HIV-1 primary infection is asymptomatic in more than half of all cases, although it could go unnoticed, as its symptoms are similar to those of common viruses, and it usually delays diagnosis. Therefore, this should be suspected in all seronegative patients with HIV-1 risk practices and compatible symptoms. Acute HIV-1 infection is usually detected 1-2 weeks later by this technique usually have a low VL (<10,000 copies/mL). The sensitivity and specificity of p24 antigenemia in plasma are 89% and 100%, respectively. In general, these patients’ VL is very high, often more than $6 \log_{10}$/mL. Clinical manifestations usually appear about 2 weeks after infection and with current ELISA testing, seroconversion can be detected 1-2 weeks later. By contrast, HIV-1 RNA can be detected in plasma the week before the onset of symp.
toms. In all these cases, HIV-1 infection should be confirmed using Western blot. In the initial phase, Western blot can be negative or show only a few bands (indeterminate); therefore, it should be repeated a few weeks later. The clinical picture of primary infection is generally similar to that of mononucleosis or viral meningoencephalitis\(^2\). The clinical manifestations are more numerous and severe the greater the VL. Fever, myalgia, night sweats, and arthralgia are common in patients with primary infection\(^3\). Acute infection (diagnosed before seroconversion) should not be confused with recent infection (less than six months duration).

At present, initiating ART during acute infection is somewhat controversial\(^4\), given that its possible benefits remain uncertain. This is due to the fact that clinical information is limited to small series, generally with no control group, and that no clinical trial has yet shown a medium- to long-term clinical benefit in reducing progression to AIDS or death, compared with initiating ART during the chronic phase\(^5\). Recent cohort studies\(^6\) have found no differences in clinical, immunological, or virological outcome in the short and medium term (3 years) among patients who initiated ART during acute infection and those who did so after acute infection (recent infection). Nevertheless, the immunological and virological outcome of both groups was better than that of patients with acute or recent infection who did not receive ART\(^7\).

**RECOMMENDATIONS**

- This committee considers that in clinical practice there is not sufficient scientific evidence to recommend ART to patients with acute HIV-1 infection. Therefore, ART is not recommended unless there are severe clinical manifestations or a prolonged duration of symptoms, once its advantages and disadvantages have been explained to the patient (level C). In the case of untreated patients, ART criteria should be re-assessed any time after 6 months, when infection is chronic. Furthermore, this committee recommends enrolling these patients in clinical trials to evaluate new therapeutic strategies. If a patient initiates ART, the same basic ART regimen must be followed (level C). In any case, a resistance test should be carried out previously because of the possibility of transmitting strains with resistance mutations (level B).

**Chronic HIV-1 infection**

**ART-naïve patients**

Treatment-naïve patients must be assessed on an individual basis as to when to initiate ART and which combination of drugs is to be used. The advantages and disadvantages of all the options must be carefully weighed up.

**When to initiate ART**

Triple ART, or HAART, has reduced the risk of progression and death of HIV-1-infected patients as the different combinations are sufficiently potent to reduce VL and lymphatic tissue to lasting undetectable limits and to enable the immune system to be restored, albeit partially\(^8\). These spectacular results, which in patients at an early stage of chronic infection can return the immune system to almost normal levels, have been marred by the medium- to long-term toxicity of antiretroviral drugs (ARD), adherence problems, resistance and the subsequent limitation of future therapeutic options, the possible transmission of resistant strains, drug-drug interactions, and the impact on quality of life\(^9\).

The current debate centers on the criteria to be used to decide when is the best time to initiate ART. The most recent evidence seems to favor an early start, although it should be understood that the definition of early or late is totally arbitrary and has varied over time. At present, the limit between early and late has been set at 350 CD4+ lymphocytes/µL.

**RECOMMENDATIONS**

- The initiation of therapy should be based more on the CD4+ lymphocyte count than on VL. We must bear in mind that the depletion of CD4+ lymphocytes is faster when VL levels are higher; therefore, this should be monitored more closely in patients whose VL is higher. VL can help to take decisions in specific situations, particularly when the CD4+ lymphocyte figure is between 200 and 350 cells/µL.

In patients with a CD4+ lymphocyte figure below 200 cells/µL, the clinical benefit of receiving ART is clear. Waiting until CD4+ lymphocytes are below 200 cells/µL can expose the patient to the risk of opportunistic diseases.

- No clear difference in immune and/or virological or clinical response has been observed between patients who initiate ART when their CD4+ lymphocytes are between 200 and 350 cells/µL and those who start therapy when the CD4+ lymphocyte figure is higher than 350 cells/µL, although more recent studies have shown a greater tendency (non-significant) towards progression to AIDS and death in patients who start ART when their CD4+ lymphocyte count is between 200 and 350 cells/µL (especially if the CD4 percentage is below 15%) than in those who start therapy with more than 350 cells/µL.

**RECOMMENDATIONS**

- The decision to start ART should be based on three elements: symptoms, CD4+ lymphocyte count, and VL.
- Patients with a symptomatic HIV-1 infection (events classed as B and C by the CDC)\(^10\) should initiate ART in all cases (level A). If the patient has an acute opportunistic infection, ART can be delayed for a few weeks, clinical circumstances permitting.
- For patients with an asymptomatic infection, the time to start therapy will be based on the number of CD4+ lymphocytes/µL and on VL (table 2).
- Patients with a CD4+ count of < 200 cells/µL should initiate ART (level A).
- Patients with a CD4+ count of between 200 and 350 cells/µL should start ART in most cases (level B). Physicians should bear in mind that current evidence tends to favor initiating ART closer to 350 cells/µL than to 200 cells/µL. Nevertheless, therapy could be delayed in those patients whose CD4+ lymphocytes remain stable at approximately 350 cells/µL and whose VL is low (more or less below 20,000 copies/mL).
3. Patients with a CD4+ of >350 cells/μL can delay initiating therapy (level B).

The time to initiate ART should always be decided on an individual basis taking previous considerations into account. Before the decision is made, at least two CD4+ and VL determinations should be performed to confirm the results. Furthermore, the patient should be prepared to initiate ART, by discussing the different options, trying to adapt the schedule of therapy to the patient’s lifestyle, and evaluating the risk of poor adherence.

**Which combination of antiretroviral drugs should be used?**

At present, the first-choice ART regimen is a combination of three drugs including two NAs and a boosted PI or an NN (table 3). Most of these combinations allow a VL of <50 copies/mL to be reached at 48 weeks in 60-70% of cases.

These guidelines consider “preferential regimens” those that are backed by data from a larger number of long-term clinical trials, with optimal efficacy and durability, acceptable tolerability, and which are easy to use. “Alternative regimens” are considered to be those that have already proven their efficacy in clinical trials, but with a lower number of patients or for a shorter period of time, or which are less efficacious, more toxic, or more difficult to take. In any case, the choice of regimen must be made on an individual basis and must be based on the potential advantages and disadvantages. The following factors should be taken into account: degree of immunosuppression and baseline VL, adherence, complexity of posology, possible dietary restrictions, presence of comorbidity, type of secondary effects that may result in the short, medium and long terms, potential pharmaco kinetic reactions and possible therapeutic options in the case of failure. At present, we have several regimens that are equally efficacious. In this context, this committee wishes to stress the growing importance of choosing a treatment that is comfortable for the patient.

### TABLE 2. Indications for antiretroviral therapy in asymptomatic patients with chronic HIV infection

<table>
<thead>
<tr>
<th>CD4 lymphocytes</th>
<th>Asymptomatic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 200</td>
<td>Always recommend</td>
</tr>
<tr>
<td>200-350</td>
<td>Recommend on most occasions*</td>
</tr>
<tr>
<td>&gt; 350</td>
<td>Refer</td>
</tr>
</tbody>
</table>

*In general, patients with a CD4+ lymphocyte count of between 200 and 350 cells/μL should initiate ART, especially if the number of CD4 is below 140. However, in certain circumstances ART could be deferred if the CD4+ lymphocyte remains stable at approximately 350 cells/μL and viral load is low (< 20,000 copies/μL).

### TABLE 3. Combinations of antiretroviral therapy in treatment-naïve patients

<table>
<thead>
<tr>
<th>Possible combinations</th>
<th>Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred regimens</td>
<td>One drug from column A + one from column B + one from column C</td>
</tr>
<tr>
<td></td>
<td><strong>A</strong></td>
</tr>
<tr>
<td>Temovir (TDF)</td>
<td>Lamivudine (3TC)</td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>Zidovudine (AZT)</td>
</tr>
<tr>
<td>Alternative regimens</td>
<td>Didanosine (ddI)</td>
</tr>
<tr>
<td></td>
<td>Stavudine (d4T)</td>
</tr>
<tr>
<td>Regimens for when PI or NN cannot be used</td>
<td>ABC + 3TC + AZT</td>
</tr>
<tr>
<td>Contraindicated regimens</td>
<td>Regimens with unboosted SQV</td>
</tr>
<tr>
<td></td>
<td>Regimens with some combinations of NA (3)</td>
</tr>
<tr>
<td></td>
<td>ABC + 3TC + TDF</td>
</tr>
<tr>
<td></td>
<td>ddI + 3TC + TDF</td>
</tr>
<tr>
<td></td>
<td>d4T + ddI + ABC</td>
</tr>
</tbody>
</table>

*The table has been drawn up from the results of clinical trials and the majority consensus of the expert committee.

**Preferred regimens**

- Available data suggest that FTC and PI can be used indiscriminately (level C). The NA combinations of choice as part of initial triple regimens are TDF + FTC + ABC or TDF + FTC + ddI or TDF + FTC + AZT. The choice of each of these combinations will depend on the third drug chosen and the safety profile (level A). Of the 2-NA combinations of choice as part of initial triple regimens, TDF + FTC in combination with efavirenz has proven superior to AZT + FTC. The latter combination is efficacious and there is wide clinical experience. The order in which the drugs appear reflects the majority feeling of the experts. Depending on the third drug chosen, there are some NA combinations of choice with which there is no experience (ABC + FTC with nevirapine; lamivudine or with atazanavir/r). There is no experience with TDF + TDF in combination with a PI as initial therapy, but there is with TDF + FTC in combination with nevirapine. The combination of d4T + FTC is efficacious, but alterations in lipid metabolism, lipodystrophy, and peripheral neuropathy mean that it is considered an alternative regimen. The combination of d4T + ddI must be avoided due to toxicity, and it is not recommended during pregnancy (risk of severe lactic acidosis, with pancreatitis or hepatic steatosis). The combination TDF + ddI is not recommended due to its greater toxicity and lower efficacy.

*In one study, EFV was proven to have a lower risk of failure than LPV/r (level A). Fosamprenavir has proven to be non-inferior to LPV/r, but it has not been compared with EFV. This committee considers that the global risk/benefit balance favors EFV over NVP (level C). NVP shows greater toxicity and has not been tried with current NAs. **Atazanavir has not been approved (or evaluated) by the EMEA for treatment-naïve patients and its efficacy has been proven with AZT + FTC. It can be administered comfortably (once daily) and seems to have a good lipid profile. It is preferable to use boosted PI.**

Consulting the text will make for a better interpretation of the table.
tance of the cost of ARD when setting up preferred treat-
ment schedules.

With respect to the different combinations of ART, this committee wishes to make several points. First: most ex-
perience in patients with advanced immunosuppression
(CD4+ lymphocyte count < 100 cells/L) is with combina-
tions of NAs with lopinavir/ritonavir (LPV/r) or efavirenz
(EFV)1-3. Second: regimens composed of 3 NAs are less
efficacious than regimens composed of 2 NAs + 1 NN10
and there are data indicating that they are less efficacious
than 2 NAs + 1 PI in patients with a very high VL11-15.

Third: there is little clinical experience with the combina-
tion of ARD from the three families (NA, NN and PI); al-
though this ART can be very potent, its complexity, toxic-
y and limited options in case of failure mean that it cannot be recommended as initial therapy1-3. The same is true for regimens including only one PI1-4. Fourth: the combination of an NN and a PI has proven to be as efficacious as triple therapy with PIs in a recent study2, although this was not the case in others16,18, and it could even be more toxic in its impact on lipid me-
tabolism2,19. Fifth: fusion inhibitors (FI), such as enfuvir-
tide (T-20), are not used in initial therapy and should be
limited to patients whose previous regimens have failed. Sixth: the evidence does not show that using more than three ARDs for initial therapy produces better results than the traditional three-drug regimen11-14.

RECOMMENDATIONS

• For initial therapy, 2 NAs + EFV or 2 NAs + 1 boosted
  PI can be used (the preferred NAs, boosted PIs and NNs
  are detailed in the following sections). The combination of
  3 NAs (zidovudine + lamivudine + abacavir) is an alterna-
  tive when the previous regimens cannot be used (level A
  (table 3).
• For the patient about to begin ART for the first time,
  regimens based on one NN are generally better than regi-
  mens based on a boosted protease inhibitor (PI/RTV) with
  low-dose ritonavir (RTV): 1) High efficacy proven in nu-
  merous clinical trials, 2) Low pill burden (soon one pill)
  makes them easier to use, 3) Fewer serious pharmacoki-
  netic interactions, 4) More favorable metabolic profile, 5)
  Lower cost. In addition to these advantages, it must be
  stressed that, thanks to their low genetic barrier, NNs are
  less associated with resistance than NNs in cases of
  primary resistance and in patients exposed to prolonged
  and repeated periods of non-adherence to ART16-18.

Nucleoside analog reverse transcriptase inhibitors
(NA) and nucleotide analogs (NtA)

In Spain, 7 NAs are commercialized: ZDV, didanosine
(ddI), zalcitabine (ddC), stavudine (d4T), lamivudine
(ddI), zalcitabine (FTC) and abacavir (ABC). One NtA,
tenofovir DF (TDF), is also commercialized. For practical
purposes in these guidelines, the abbreviation NA in-
cludes TDF. ddC will shortly be taken off the market.

For initial therapy, 2 NAs + EFV or 2 NAs + 1 boosted
PI can be used (the preferred NAs, boosted PIs and NNs
are detailed in the following sections). The combination of
3 NAs (zidovudine + lamivudine + abacavir) is an alterna-
tive when the previous regimens cannot be used (level A
(table 3).

• The main advantage of PI/RTV is their high genic bar-
  rier to the development of resistance. This high genetic
  barrier makes them more attractive than NNs in cases of
  primary resistance and in patients exposed to prolonged
  and repeated periods of non-adherence to ART16-18.

The combination of choice are TDF + FTC, ABC + 3TC and
ZDV + 3TC, since their tolerance and efficacy have proven
acceptable in several clinical trials. Furthermore, avail-
able data show that either FTC or 3TC can generally be
administered. It must be stressed that these three combi-
nations present very different toxicity profiles. ZDV has a
greater risk of causing lipoatrophy than TDF19-23. Between
5% and 8% of patients treated with ABC develop a hyper-
sensitivity reaction whose incidence will probably de-
crease with the genotyping of HLA-B*5701. Many reports
of isolated cases and some cohort studies reveal deterio-
ration in the renal function of patients exposed to TDF,
which is generally associated with other nephrotoxic fac-
tors, although this has not been proven in clinical trials.

Combinations with ZDV + 3TC or ABC + 3TC may be
an alternative, although information is scarce. The only
data on the combination ddI + FTC come from a clinical
trial20, therefore the safety profile of this combination has
not been firmly established.

The combination d4T + 3TC has proven its efficacy in
several clinical trials, but it is only considered as an alter-
native regimen today due to its greater toxicity. The com-
bination d4T + ddI is not recommended due to its potential
greater long-term toxicity and it is contraindicated (as
long as there are alternatives) in pregnant women due to
the risk of severe, even fatal, lactic acidosis with pancre-
atitis or hepatic steatosis17-19. The combination TDF + ddI
must not be administered at all due to its greater toxicity
and lower efficacy21-25. The committee considers that
ZDV + d4T should not be administered because of antago-
nism and that ddC should not be administered with any
NA because of toxicity associated with ddC24-26. Neither is
it recommended to use FTC with 3TC, since they have a
similar resistance profile and probably have few associat-
ed clinical benefits.

In any case, the final choice of combination of NA must
be on an individual basis taking into account the charac-
teristics of the drug, clinical situation, and patient prefer-
enes. Easy regimens can facilitate adherence. These in-
clude drugs that can be administered once daily (ABC, ddI,
FTC, 3TC and TDF) or coformulated with fixed doses (e.
.g., TDF + FTC, ABC + 3TC, and ZDV + 3TC). Fixed dose com-
binations probably improve adherence, although it is ar-
guable whether this advantage is clinically relevant18-19.

The combination ZDV + 3TC is a simple, efficacious reg-
imen with wide clinical experience. Its cost, in coformu-
lated tablets, is lower than that of coformulations of
TDF + FTC or ABC + 3TC. The combination ABC + 3TC is
equivalent to ZDV + 3TC20. There is no clinical trial expe-
rience with the combination ABC + 3TC with nevirapine
(NVP) or with atazanavir (ATV). TDF + 3TC is efficacious
in combination with EFV20-23. No studies have been carried
out on TDF and 3TC in combination with a PI as initial
therapy, but there have been studies on TDF with FTC
(in combination with lopinavir boosted with ritonavir
(LPV/r))19-23. The combination TDF + 3TC is more effica-
cious than AZT + 3TC when associated with EFV, al-
though the difference seems to be due essentially to the
lower toxicity of the former in the short term and re-
term19. There is no experience with the combination
TDF + 3TC (or FTC) plus NVP. In general, it is reas-
nable to extrapolate the results obtained with 3TC to those
ob-
tained with FTC and vice versa (level C).
The combination d4T + FTC associated with EFV, is superior to d4T + EFV89. There is no experience with the combinations d4T + FTC nor with NVP nor with PI. The combination d4T + 3TC has proven its efficacy in several studies, although it produces more alterations of lipid metabolism, lipodystrophy, and peripheral neuropathy than the combination TDF + 3TC110. Therefore, the combination d4T + 3TC is considered an alternative regimen. In addition to TDF + 3TC or FTC, ABC + 3TC and d4T + FTC, other combinations of NA could be used in one-daily regimens, although their long-term virological efficacy has not yet been determined (d4T + 3TC)69,72.

**Recommendations**

- The combinations of NAs and/or NtAs of choice for initial triple regimens are TDF + FTC (or 3TC), ABC + 3TC (or FTC) or ZDV + 3TC (or FTC) (level A). The choice of one of each of these combinations will depend on the third drug chosen and on the safety profile (level A). Physicians must bear in mind that a clinical trial111 has shown a greater risk of developing lipodystrophy in patients treated with ZDV than in patients treated with TDF (level A). Although there are no clinical trials that directly compare the development of lipodystrophy in patients treated with ZDV or ABC, evidence from other trials111-113 suggests that ABC is similar to TDF with regard to the risk of developing lipodystrophy. Other alternatives are d4T + FTC or 3TC, d4T + 3TC and ZDV + d4T. Available data suggest that FTC and 3TC can be used indistinctly (level C). The combinations d4T + d4T and TDF + d4T must be avoided due to their toxicity and lower efficacy. The following combinations are not recommended: ZDV + d4T, 3TC + FTC and d4T + any other NA. Prudence is recommended with combinations of NAs and/or NtAs that have not been studied in clinical trials.

**ART combinations with three NA**

Combinations of 3 NA have shown virological and immunological efficacy in several studies. Although regimens with 3 NA are easier to take and have fewer drug-drug interactions than other combinations, several trials have shown that this regimen is less efficacious than regimens with NNs or PIs68,69. Therefore, the combination ZDV (or d4T) + 3TC + ABC should only be used in treatment-naive patients as an alternative to a regimen with NN or PI when these cannot be used due to problems of toxicity, interactions with other drugs, or complexity of the regimen. It is not recommended to use d4T + d4T + ABC as initial therapy111. Furthermore, combinations of 3 NAs that include ABC + 3TC + TDF or d4T + 3TC + TDF should not be used in any patient112,114.

The combination ZDV + 3TC + ABC is available in a commercial presentation that enables it to be administered in one tablet twice daily. This makes it an attractive regimen in terms of adherence.

**Recommendations**

- A regimen with ZDV + 3TC + ABC should only be used when it is not possible to use a regimen with NNs or PIs as initial therapy (level A). It is not recommended to use d4T + d4T + ABC as initial therapy (level A). The committee also recommends not using at any time 3-NA regimens containing abacavir + 3TC + TDF or d4T + 3TC + TDF (level A). There is not enough experience to make recommendations with other combinations of 3 NAs and/or NtAs.

**Non-nucleoside reverse transcriptase inhibitors**

Only two NNs are commercialized in Spain: NVP and EFV. Both drugs are cytochrome P450 inducers; therefore, they can cause pharmacokinetic interactions. EFV is administered once daily (one 600 mg capsule). This drug is contraindicated during pregnancy117. NVP should be administered as follows: one 200 mg tablet daily for 14 days and then one 200 mg tablet twice daily. In the 2NN study, NVP administered once daily seemed to be as efficacious as NVP twice daily, although the study was not powerful enough to evaluate the non-inferiority of NVP QD compared with EFV. Furthermore, greater liver toxicity was observed with this regimen117. These drugs must be used in potent combinations, since, if VL is not completely suppressed, there may appear mutations that induce cross-resistance to all the drugs in this family16.

To date, it has been shown that regimens with EFV or NVP are more efficacious than those with 3 NAs70,78. Furthermore, several studies have shown that a regimen with EFV is more efficacious than a regimen with some PIs (indinavir [IDV]114, saquinavir boosted with ritonavir [SQV/r]118, amprenavir boosted with ritonavir [APV/r]118, LPV/r121). No studies have compared NVP or EFV with fosamprenavir (FPV/r). No clinical trials have shown that NVP is more efficacious than a PI. Finally, comparison of these two drugs has not enabled us to draw definite conclusions122.

In addition to these considerations, when choosing an NN the following should be taken into account: 1) EFV is contraindicated in pregnant women due to the risk of teratogenicity. It should also be avoided in women who do not use safe contraception or who wish to become pregnant. Similarly, it should be avoided in patients with a history of severe psychiatric conditions. EFV can produce dizziness, confusion disorders and/or amnesia. Patients should be informed that, if they present these symptoms, they should avoid potentially dangerous tasks such as driving or using machinery. 2) Severe, and even fatal liver events have been described with NVP; these occur during the first weeks of therapy. In addition to an increase in transaminases, approximately half the patients also develop cutaneous exanthema, with or without fever or flu-like symptoms. Therefore, NVP should be administered with extreme caution in patients with chronic liver disease and elevated transaminases, and it is contraindicated when transaminases are more than five times the upper limit of normal. The first 18 weeks of therapy with NVP are critical and require close monitoring of patients in order to spot the potential onset of severe cutaneous reactions (including the Stevens-Johnson syndrome and toxic epidermal necrolysis) that may be a risk to life or severe hepatitis/hepatic insufficiency. The greatest risk of these reactions appears during the first six weeks of therapy. However, the risk of hepatic problems remains after this period and monitoring should be maintained at subsequent intervals. Women and patients with a high CD4+ lymphocyte count have an increased risk of adverse liver reactions. A greater incidence of symptomatic liver problems has been observed in women with a CD4+ lympho-
cyte count of > 250 cells/µL compared with those who have a count of < 250 cells/µL (11% vs. 0.9%). Similarly, an increased risk has been reported in men with a CD4+ lymphocyte count > 400 cells/µL compared with those who have lower counts (6.3% vs. 1.2%). In some cases, liver damage has progressed despite discontinuation of therapy. Patients who develop signs or symptoms of hepatitis, severe cutaneous reaction, or hypersensitivity reaction must interrupt therapy with NVP. Therapy with NVP should not be re-initiated after severe hypersensitivity, cutaneous, or liver reactions. Liver tests should be monitored every two weeks for the first two months of therapy, at the third month, and regularly thereafter. This monitoring of liver tests should be closer if patients present signs or symptoms suggestive of hepatitis and/or hypersensitivity or if GOT or GPT values are > 2.5 times the upper limit of normal before or during therapy. NVP should not be administered to patients with GOT or GPT values > 5 times the upper limit of normal before therapy until baseline GOT/GPT values stabilize (Viramune, SPC). Special care must be taken with EFV and NVP in patients on methadone, since their dose of methadone usually has to be increased.

**Recommendations**

- This committee considers that the global risk/benefit balance favors EFV to NVP (level C). The choice of a drug should take into account the risks associated with specific toxicity. NVP is not recommended in women with a CD4+ lymphocyte count of < 250 cells/µL or in men with a count of > 400 cells/µL. NVP should be used with extreme caution in patients affected by hepatotropic viruses.

**Protease inhibitors**

In Spain, 8 PI are commercialized: saquinavir (SQV), indinavir (IDV), ritonavir (RTV), nefinavir (NFV), fosamprenavir (FPV), lopinavir (LPV), atazanavir (ATV) and tipranavir (TPV). ATV boosted with ritonavir and TPV boosted with ritonavir are only approved by the EMEA for treatment-experienced patients. PIs are cytochrome P450 inhibitors, and can therefore cause pharmacokinetic interactions. They are included in triple regimens with two NAs, these triple combinations being the ones with which there is more experience6. The final choice of PI is based on efficacy, tolerance, interactions, posology and pharmacokinetics.

Full-dose IDV, NFV and RTV should only be used in treatment-naïve patients in exceptional cases owing to their lower efficacy and/or greater toxicity and/or greater complexity of use. This committee recommends habitual use of RTV-boosted PIs for treatment-naïve patients.

FPV is a produg of amprenavir, which makes it possible to reduce the number of daily capsules both when used as the only PI (two 700 mg capsules BID) and when boosted with RTV (one 700 mg capsule + 1 ritonavir capsule BID, or two 700 mg capsules + 2 ritonavir capsules QD, although the latter dosage may be less efficacious, especially in naïve regimens). The dose of FPV recommended by the EMEA is 700 mg BID with 100 mg of RTV BID.

ATV is an azapeptide PI that is administered once daily. The recommended dose of ATV is 300 mg (it is presented in 100 mg, 150 mg, 200 mg hard-gel capsules—300 mg capsules will soon be available) administered with 100 mg of RTV once daily with meals. It has fewer adverse metabolic effects than other PI, particularly when taken unboosted with RTV. If ATV is administered with EFV or TDF, its exposure is reduced. The doses of ATV/r are 400/100 mg when taken with EFV and 300/100 when combined with TDF.

**ART combinations that include boosted PI**

The use of small doses of RTV (the PI with the strongest cytochrome P450 inhibitory effect) inhibits the metabolism of the second PI and improves its pharmacokinetic profile. The combination of a PI boosted with RTV makes it possible to reduce the pill burden and use once-daily or twice-daily dosing with meals, which favors adherence to ART. Furthermore, it improves the Cmin/C50 ratio of the second PI. Thus, resistance could be avoided. These combinations of PI have the disadvantage that they can boost toxicity.

LPV/r was the first fixed-dose coformulation of 2 PIs, and its virological and immunological efficacy has been maintained in a seven-year study10. Once-daily LPV/r (6 capsules) has proven to be as efficacious as administration every 12 hours, although with a greater frequency of diarrhea10. To date, it has been administered in three capsules (400 mg/100 mg) every 12 hours. The EMEA has approved a new pharmaceutical formulation of LPV/r in coformulated tablets containing 200 mg of LPV and 50 of RTV. The recommended dose is two tablets every 12 hours. Pharmacokinetic data support a lower interindividual variability in the plasma concentrations of lopinavir and a lesser effect of food intake11. Furthermore, with this new presentation, it is not necessary to refrigerate the tablets, even if they are to be stored for more than one month (RTV must be kept in the refrigerator if it is to be stored for more than 30 days or if the room temperature is higher than 25 °C). No data are available yet on the tolerance/toxicity of the new tablets compared with the capsules.

In treatment-naïve patients, studies12,13 show that a PI (LPV, SQV, FPV, ATV) boosted with RTV has efficacy and barrier advantages against the development of resistance compared with unboosted PI. The main disadvantage of boosting with RTV is the increased risk of adverse effects, but this is compensated by a marked increase in its antiviral potency and in the genetic barrier against resistance.

**Recommendations**

- The committee recommends LPV/r and FPV/r as first-choice PIs (level A). Both have a similar antiviral activity and metabolic and tolerance profile. ATV/r and SQV/r are alternatives, and, although they can be as efficacious as LPV/r (level C), this committee considers them as alternatives until comparative data from clinical trials with LPV/r become available. TPV/r should not be used in treatment-naïve patients (level A).

**Treatment-experienced patients**

The usual reasons for changing ART are therapeutic failure, toxicity or intolerance, lack of adherence, or simplification of a complex regimen. In this section, we shall...
discuss the scientific evidence supporting the current recommendations on the modification of ART in a patient whose therapy is failing. The remaining reasons for modifying ART are discussed in other sections of these guidelines and in the extended document available on the web pages of GESIDA and the PNS.

**Failure of ART**

The failure of ART can be defined from a clinical, immunological, and virological standpoint. The criteria for each of these types of failure have been described in section 2. Unless stated otherwise, when we speak of therapeutic failure, we are referring to virological failure.

The incidence of therapeutic failure, its causes, and the profile of selected resistance mutations have changed over the 10-year history of ART. The early ART period (1996-1999) was characterized by a generalized use of complex and toxic combinations of NAs and unboosted PIs in patients who had often received suboptimal therapy with NAs. Observational studies that analyzed the appearance of virological failure during the early years of ART reported 20% to 60% incidence in patients taking their first ART. Some patients who currently suffer from multi-resistant HIV-1 infection are from this period. Since 1999 (recent ART) and coinciding with the introduction of NNs and PIs boosted with low doses of RTV (PIV), the incidence and characteristics of the failure of early ART have changed substantially. Several studies show a lower incidence of therapeutic failures after the introduction of NNs as a component of ART. The modern ART era shows a generalized preference for very simple regimens combining non-thymidine NAs and NNs or PIs, all of which will lead to a change in the profile of the selected resistance mutations during the first virological failure, i.e., it will reduce the incidence of thymidine analog mutations (TAMs) and mutations of the protease gene, by increasing resistance mutations against NNs, i.e., K65R selected by TDF and ABC, L74V selected by ABC and, especially, M184V/V135.

**Factors affecting therapeutic failure**

The factors affecting failure of ART are very diverse although they can be classified in 3 broad groups depending on the patient, drugs, or the virus. In the first group, adherence to treatment is the most important and has been identified as an excellent predictor of therapeutic response, both in the context of clinical trials and in cohort studies.

The most important drug-dependent factor is the potency of the regimen. Other factors are defective absorption of the drug and pharmacological interactions.

The most important virus-dependent factor is resistance to antiretroviral drugs as a result of the enormous replication capacity of HIV-1, its wide diversity, and pharmacological pressure. Resistance to antiretroviral drugs can be transmitted to other people and can be detected in up to 12% of recent HIV-1 infections. Two cohort studies published a few years ago agree that if a VL of 50 copies/mL is reached after the first ART, a rebound in VL is usually associated with poor adherence or with adverse reactions, and very rarely with a genuine failure of therapy, i.e., due to a lack of potency, drug-drug interactions, or problems of absorption.

**Criteria for changing ART due to therapeutic failure**

Decisions on whether to change therapy because of failure are usually based on virological criteria (Section 2), except in the particular situation of a patient with multi-resistant HIV-1 infection (see below). As a general principle, in the case of a virological failure, therapy should be changed as soon as possible to avoid an accumulation of mutations and an increase in VL, thus facilitating the response to new treatment.

In some patients with ART and suppressed VL, rebounds or transient elevations of VL (blips) can be observed just above the threshold for detection. In most studies, these rebounds are not associated with a greater risk of failure, i.e., due to virological failure. Occasionally, some patients with suppressed VL maintain a decreased CD4+ lymphocyte count. In these cases ART should not be changed, except for combinations leading to a decrease in the number of CD4+ lymphocytes, e.g., TDF + ddl. Treatment with IL-2 should be considered.

Clinical failure in a patient taking ART, i.e., the appearance of clinical B or C events associated with progression of HIV-1 infection, is not always associated with virological failure. These events sometimes appear after the first months of ART in very immunodepressed patients, or are associated with immune restoration. Tuberculosis or the malignant lymphoproliferative processes that are often diagnosed in HIV-1-infected patients can oblige efficacious ART to be modified in order to avoid the pharmacological reactions and toxicity that are common to the different drugs the patient has to take.

**General recommendations on changing ART due to virological failure**

- A change in ART due to failure must be made early in order to avoid the accumulation of mutations and an increase in VL, thus facilitating the response to new therapy (level C). The only exception to this recommendation is multi-resistant HIV-1 infection.
- In the case of virological failure, a resistance test should be carried out to design the best therapeutic regimen (level B). The resistance test should be carried out while the patient is receiving therapy or during the 4 weeks after its discontinuation.
The choice of new ART after therapeutic failure makes it necessary to analyze the causes, especially when the failure is due to adherence to ART or drug-drug interactions. The results of previous resistance tests (if any) should be taken into account, the complete pharmacological history should be known, and any possible toxicity to specific antiretroviral drugs should be noted (level C).

Transitory elevations in VL of between 50 and 500 copies of viral RNA (blips) do not make it necessary for ART to be changed (level B).

**Change of ART after the first failure (second-line therapy)**

Few randomized clinical trials have evaluated the efficacy of the different combinations of antiretroviral drugs in second-line therapy.

The objective of therapy in this situation is to achieve a reexpression of VL. Therefore, the change in ART should not be delayed, resistance testing should be performed\(^{147}\), and three active drugs should be introduced depending on the results.

The following situations can occur depending on initial ART: failure with 3 NA, with 2 NAs and 1 NN or with 2 NAs and one PI (table 4).

**Change to ART after the first failure of a regimen containing 3 NAs**

No randomized trials have tackled this problem. In patients who fail after initial therapy with ZDV, d3TC and ABC, the most common mutation is M184V\(^{87}\). Patients who have initiated ART with 3 non-thymidine NAs often develop mutation M184V and can select K65R\(^{148,149}\). In these cases, two thymidine analogs (ZDV and d4T) NAs and PIs remain active. Furthermore, it is well known that patients with previous failures to NAs are hypersusceptible to EPV, which favors the virological response if we add this drug to the new treatment\(^{150}\). An ART regimen with 2 active NAs in the resistance test with an NN and a boosted PI can be efficacious in this situation of failure. Therapy with four drugs (2NAs, 1NN and 1PI), while possibly more efficacious, runs the risk of having greater toxicity, worse adherence, and fewer future possibilities of rescue.

**RECOMMENDATIONS**

Second-line therapy in this situation of virological failure would be:

- Two new NAs (chosen depending the result of the resistance tests) with 1 NN (level C) or a PI boosted with RTV (level C), or with an NN and a PI, preferably boosted with RTV (level C). If the latter option is chosen, we must bear in mind that adherence can be more difficult.

**Change of ART after the first failure of a regimen containing 2 NAs and 1 NN**

NAs, especially EFV, are the most widely used drugs in initial ART. A single mutation (e.g., 103V) is capable of generating high-level resistance to one or all NNs, which usually occurs when there is incomplete suppression of HIV-1 replication\(^{151}\). This is often accompanied by other mutations conferring resistance to NA (basically M184V, and, less commonly, TAMs, L74V or K65R).

**RECOMMENDATIONS**

- The most reasonable therapy is a regimen with 2 new NAs (depending on the resistance test) and a PI boosted with RTV (level C). This option has proven to have antiviral efficacy in patients who have already been treated with 2 NAs, and therefore these drugs are expected to have a similar effect in patients treated with 2 NAs and 1 NN.

**Change in ART after the first failure with a PI-containing regimen**

During the early ART era, failure with 2 NAs and 1 PI occurred relatively often, either due to toxicity or poor adherence\(^{152}\). Fortunately, the currently generalized use of PIs has reduced the incidence of virological failure when an initial PI is used.

PIs are slightly different with respect to the other antiretrovirals and this has important implications for the development of therapeutic failure. First, the efficacy of PIs may depend on pharmacokinetic factors\(^{153,154}\). Second, the development of resistance to PIs is a gradual process that normally requires the accumulation of several mutations in the protease gene\(^{155}\), which may confer class resistance to PIs. The appearance of resistance is an ongoing phenomenon that leads to progressive reduced susceptibility of viral strains to PIs. There are also mutations selected by some PIs that do not present cross-resistance with others: 30N (NFV\(^{156}\), and 50L (ATV\(^{157}\). The combination of a PI (LPV, SQV, IDV, APV, FPV, ATV and TPV) with low doses of RTV can increase the plasma concentration of the PI, improve dosing and adherence, and reduce the incidence of mutations of resistance to PIs\(^{158}\). The introduction of a fixed-dose combination of LPV/r in the year 2000 proved very efficacious in patients with a history of therapeutic failures with NNs or PIs. Undetectable and durable VL was achieved in a significant number of patients\(^{159,160}\). Furthermore, when virological failure is detected in a patient receiving a regimen containing boosted PIs, mutations may not be

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**TABLE 4. Possible therapeutic regimens in patients who experience virological failure after their first ART regimen**

<table>
<thead>
<tr>
<th>Previous regimen</th>
<th>New regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 NAs</td>
<td>2 NAs + NN or PI/r(^a)</td>
</tr>
<tr>
<td>2 NAs + 1 NN</td>
<td>2 NAs + PI(r)s(^a)</td>
</tr>
<tr>
<td>2 NAs + PI or PI(r)(^b)</td>
<td>2 NAs + 1 NN(^c)</td>
</tr>
</tbody>
</table>

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*The choice of new NA must be based on a resistance test*

*The choice of PI must be based on a resistance test.*

*In a previous failure with NA in patients naive for NN, inclusion of an NN (d3TC) in the new therapy improves the virological response.**

*When a PI is used in the initial regimen and the diagnosis of virological failure is early, mutations may not be detected in the protease gene. In this case, the 2 NAs must be changed. The PIs can be maintained unless there is intolerance, toxicity or poor adherence.

*NN nucleoside/nucleotide reverse transcriptase inhibitor; NT: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor boosted with ritonavir.*

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detected in the protease gene, although they may be detected in the reverse transcriptase gene. The use of a second boosted PI may be a valid alternative as second-line therapy, especially if the change is made quickly and the accumulation of numerous mutations in the protease gene is not permitted.

Another simple and efficacious regimen consists of a combination of 2 new NAs and 1 NN. The lack of cross-resistance between PIs and NNs, as well as hypersusceptibility to NNs in patients with a certain degree of resistance to NNs, speaks in favor of this combination as second-line therapy after a first failure with a PI. Several studies have shown that, in patients exposed to PIs and NNs and not exposed to NNs, the inclusion of an NN in the new therapy improves the virological response. If this option is chosen, the 2 NNs must be totally active and with a high genetic barrier, since an incomplete suppression of VL would lead to a rapid selection of mutations conferring resistance to NNs.

RECOMMENDATIONS

Second-line therapy in this situation of failure would involve the following:

- Two new NAs (chosen depending on the results of the resistance test) and 1 NN. This option may be attractive for patients with serious adherence problems (level C).
- Two new NAs (chosen depending on the results of the resistance test) and a PIs. This option would be limited to situations that do not involve the accumulation of resistance to the new therapy (level C).
- One or two new NAs (chosen depending on the results of the resistance test) with a PIs and an NN. This alternative is indicated for patients who have not had adherence problems and in whom failure has been caused mainly by problems of antiviral potency, pharmacokinetics, or resistance (level C). NNs and PIs should be chosen according to the results of the resistance test.

Change of ART after more than one therapeutic failure (rescue therapy)

Definition

Treatment failure of at least two lines of ART is known as rescue therapy. In this situation, and with the exception of those patients who started therapy with 3 NAs, most patients have experienced failure with the three most common families of antiretroviral drugs: NNs, NAs, and PIs.

Objective of therapy

The objective of therapy in this population is to achieve once again maximum viral suppression (< 50-400 copies/mL). Therefore, there must be at least two active drugs in the new regimen, which must also contain other previously used drugs that conserve some activity in the resistance test and are well tolerated by the patient. This objective is currently possible with the new drugs available, although the percentage of successes falls as the number of accumulated failures increases.

In this situation, it is important not to delay the change in therapy, since continued use of the failed regimen only helps to increase VL and accumulate a greater number of mutations in the protease and reverse transcriptase genes. Several strategies help achieve re-suppression of VL.

- Make adherence easy. New ART must be comfortable and well tolerated. In patients with multiple failures of therapy due to difficulties of adherence, the administration of simple regimens, such as ZDV/3TC/ABC + TDF, can achieve unexpected results. Furthermore, directly observed treatment strategies, which are currently available thanks to the large number of RDs, may prove useful in specific populations.
- Resistance testing. A genotypic or phenotypic resistance test with each virological failure can optimize the new treatment, increase its efficacy, and improve prognosis.
- Genotypic inhibitory quotient. The development of resistance to PI is progressive and related to the successive accumulation of mutations in the protease gene. The increase in mutations requires an increase in the concentration of the drug necessary to suppress viral replication. The genotypic inhibitory quotient (GIQ) is the ratio of the plasma concentration of the drug to the number of relevant mutations in the protease gene, and is currently considered a predictive marker of response to therapy with PIs. In general, having > 5 mutations in the protease gene significantly reduces the efficacy of PIs.
- Monitoring of drugs in plasma. The interindividual variability of the plasma concentrations reached with PI and the interactions between antiretroviral drugs and other active ingredients mean that, occasionally, the expected plasma levels are not reached. This is especially important in rescue therapies, which use several antiretroviral drugs with unknown pharmacokinetic interactions that can lead to an insufficient plasma concentration. Therefore, monitoring of drugs in plasma can improve the efficacy of treatment, e.g., with 2 boosted PIs, and may require dose adjustment. It may also be useful if the objective is to increase the PI dose in order to increase its inhibitory quotient.

None of these strategies has been evaluated in prospective and randomized studies with sufficient statistical power to enable them to be recommended in daily clinical practice.

ALTERNATIVES IN RESCUE THERAPY

In recent years, several clinical trials have compared different rescue therapies. These studies cannot be easily compared due to the heterogeneous nature of the study populations, the diversity of previously used drugs, the efficacy criteria used and follow-up time. Most experience has been with the new boosted PI and with T-20. Furthermore, there is interesting experience with 2 PIs boosted with RTV. With very few exceptions, NNs have not proven useful in this situation.

Boosted protease inhibitors specifically indicated for rescue therapy: Tipranavir. This is a non-peptide PI with potent in vitro activity against HIV-1 strains that are resistant to currently approved PIs. This drug has recently been approved in Spain and is indicated for HIV-1-infected patients who have received several anti-

Enfuvirtide (T-20). T-20 acts by inhibiting the fusion of HIV-1 with human cells and preventing the virus from entering them and starting its replication process. It is administered subcutaneously and its main adverse effect is a local reaction at the point of injection. Two phase III studies (TORO I and TORO II) compared the antiviral activity of T-20 as part of an optimized ART regimen with an optimized ART regimen not containing T-20. The studies included almost 1000 multi-treated patients (75% with previous AIDS) between them, with a median baseline VL >100,000 copies/mL and a median CD4+ <100 cells/μL. At 24 weeks, the fall in VL was significantly greater in the patients treated with T-20 than in those treated with the optimized ART regimen alone. T-20 produced an additional fall in VL of -0.93 log₁₀ in TORO I and of -0.78 log₁₀ in TORO II (p < 0.0001). In the combined analysis of both studies, the fall in VL at week 48 compared with baseline was -1.48 log₁₀ copies/mL for the group that received T-20 compared with -0.63 log₁₀ copies/mL for those who received the optimized therapy only (p < 0.0001). The probability of reaching a virological response, regardless of the definition used, was more than double in patients treated from the start of the study with T-20 compared with the control group: the fall in VL >1 log₁₀ was 37% compared with 17%; VL < 400 copies/mL was 30% compared with 12%; and VL < 50 copies/mL was 18% compared with 8% (p < 0.0001). Time to failure was almost triple in the T-20 group compared with the control group, 52 and 11 weeks, respectively (p < 0.0001). That is, not only the primary efficacy analysis, but also all the secondary efficacy analyses predefined in the study design showed that rescue therapy in multi-treated patients was more efficacious with regimens based on the combination of T-20 and drugs selected according to resistance testing.

In addition to the factors for virological efficacy defined elsewhere, the response at week 12 helps to predict the response to therapy. In a modified on-treatment analysis, all those patients who continue on treatment at weeks 24, 48 and 96 are evaluated, all those patients who achieved a fall ≥ 1 log₁₀ at week 12, 59.5% (95% CI: 53.6%-65.1%) maintained a VL < 400 copies at weeks 96; and 39.2% (95% CI 33.6%-44.8%) maintained a VL < 50 copies/mL compared with 2.6% (95% CI: 0.6%-6.1%) and 1.3% (95% CI: 0.3%-3.8%), respectively, in patients with no virological response at week 12.

Mutations that reduce sensitivity to T-20 have been identified in gp41 of the virus, therefore, we can expect future studies to report a correlation between specific mutations and virological response to T-20.

In summary, T-20 is the drug of choice in patients with several accumulated resistance mutations. A recent Spanish consensus on the use of T-20, whose conclusions are pending publication, recommends using it in those patients for whom an optimal 3-drug regimen cannot be designed.

Two boosted protease inhibitors. These regimens essentially consist of the combination of LPV/r with another PI, thus taking advantage of the small dose of RTV contained in the commercial combination of LPV/r which also boosts the second PI. Although attractive in theory, few studies support these combinations as rescue therapy.
Lopinavir and saquinavir. This combination is attractive because of the intrinsic potency of both drugs and thanks to the low pill burden of the new pharmaceutical presentation of SQV in 500 mg hard-gel capsules. Several studies show that there are no significant changes in the plasma concentrations of LPV and SQV when they are administered together with RTV.183,184

Lopinavir and fosamprenavir. There is a significant interaction between LPV/r and PPV that leads to a fall in the concentrations of both drugs.185,186 The clinical importance of these findings is not known with any accuracy; therefore, these drugs should not be used in combination.

Lopinavir and atazanavir. One study analyzed the pharmacokinetic and efficacy profile of the combination of LPV/r (400/100 mg BID) plus ATV (300 mg QD) in 16 patients with few therapeutic options.187 This combination achieved high plasma concentrations of both drugs, with a low toxicity potential (no patient had to suspend therapy) and high virological efficacy. At 24 weeks, 13/16 patients presented a VL of <50 copies. If these results are confirmed, this combination could prove attractive.

**Recommendations on rescue therapy**

- With currently available drugs, it is possible to achieve an undetectable VL in a high number of patients (level A). The objective of rescue therapy is to achieve once again an undetectable VL (level C).
- It is recommended to use at least two new antiretrovirals that are totally active according to the resistance test and from different pharmacological classes. These two drugs will be administered with others that the patient may have already received, but that maintain a certain degree of antiviral activity (level A).
- In patients who accumulate several resistance mutations in the protease and reverse transcriptase gene, it is advisable to carry out a genotyping study, consult updated databases on internet, or ask an expert in treating patients with multi-resistant HIV-1 infection. Obtaining CD4+ lymphocyte counts of >200/μL or a fall of at least 0.5 log10 in VL is considered a good result (level A).
- The new ART regimen should be comfortable, well tolerated, and as minimally toxic as possible. Adherence to therapy should be guaranteed before starting rescue therapy (level C).

**Treatment of HIV-1 infection in the patient with no therapeutic options**

We define HIV-1 infection as multiresistant or with no therapeutic options when it is impossible to design an ART regimen that is potentially efficacious with currently available drugs or with those that will become available in the near future.

In this population, where achieving suppression of VL is very difficult or impossible, the objective of therapy will be to preserve the immune function and avoid clinical progression of the infection. Obtaining CD4+ lymphocyte counts of >200/μL or a fall of at least 0.5 log10 in VL is considered a good result (level A), since it is usually accompanied by a slowing-down of clinical progression.

In general, virological failure in the multi-treated patient rarely leads quickly to clinical and immunological failure.12,38,109 In fact, many patients experiencing virological failure maintain stable or even greater CD4+ counts, and approximately only one third experience a fall to counts below baseline values.109

In cases where it is impossible to design a regimen with at least two potentially efficacious drugs, it is reasonable to aspire to a limited fall in VL which allows maintenance or immunological improvement and, therefore, avoidance of clinical failure while waiting for new therapeutic options.101,105 The possibility must be considered of referring these patients to a center with experimental drugs in clinical trials.

**Therapy with ≥5 antiretroviral drugs ("mega-HAART")**

One option for rescue therapy that aims for complete suppression of viral replication is the combination of a PI with five or more drugs, which has become known as "mega-HAART" (e.g. 2 boosted PIs + 2-3 NAs + NNs). Except for anecdotal studies, "mega-HAART" regimens have not shown any clinical benefit, are difficult to fulfill, have high toxicity and are expensive.

**Suspension of ART in patients with multiple therapeutic failures**

Several studies have analyzed the usefulness of temporary interruptions of ART based on the hypothesis that the reappearance of the wild-type sensitive to the drugs will facilitate a better response after reintroducing therapy. Clinical trials performed to evaluate this strategy show a marked fall in the CD4+ lymphocyte count during the interruption compared with those of patients who continue with ART and have a greater risk of clinical progression.

**Therapy with non-suppressive ART**

Several studies have shown the beneficial effects of maintaining an ART regimen that does not suppress VL (when compared with total suspension of therapy) in patients with multi-resistant HIV-1 infection, especially if they have advanced HIV-1 infection. In patients with no options for therapy, non-suppressive treatment that does not compromise the efficacy of future drugs can be chosen. Treatments that are comfortable, minimally toxic, and that somehow reduce viral capacity to replicate must be sought.

In these patients it is tempting to use ART with 3TC or FTC in order to select mutation M184V in the majority of HIV strains. In the majority of viral strain, either alone or in combination with 1 or 2 NAs or NNIs. Ex-cept for anecdotal studies, “mega-HAART” regimens have not shown any clinical benefit, are difficult to fulfill, have high toxicity and are expensive.

**Introduction of new antiretroviral drugs in advanced clinical trials**

The host therapeutic option in multi-resistant HIV-1 infection would involve the availability of new drugs aimed at new therapeutic targets and, thus, active against HIV-1. Very often, the patient’s immunological status and the appearance of new antiretroviral drugs do not allow us to wait until two active drugs are available and oblige us to introduce a new drug to a new antiretroviral regimen in which the other drugs are recovered, i.e. monotherapy. Nevertheless, for a patient with severe immunodepression (CD4+ < 100/μL) and the risk of clinical progression and death, the new drug should be introduced, since this in-
volves a transitory improvement in the patient’s immunological status.

Recommendations in multi-resistant HIV-1 infection

- It is not recommended to interrupt therapy, especially if the CD4+ lymphocyte count is < 200–300/μL (level A).
- When there is a risk of clinical progression or death and it is not possible to design therapy with two active drugs over a short period of time, ART should be administered, even if it only includes one active drug (level C). These therapies can lead to a transitory improvement in immunodeficiency and improve progress. The possibility of referring the patient to a center with experimental drugs should be considered.
- All simplification options for multi-resistant HIV-1 infection should contain 3TC or FTC in order to select and maintain mutation M184V, and thus reduce the capacity for viral replication (level C). If optimal therapy is not possible, it is advisable to maintain a suboptimal treatment. In this case, it is also indicated to maintain 3TC or FTC.

Simplification of efficacious ART

Simplification of ART is understood as changing a regimen with which absolute virological suppression has been achieved for another that maintains this suppression and that allows the regimen’s complexity to be reduced. Thus, both the patient’s quality of life and adherence can be improved. The objectives of simplification are to maintain virological and immunological control, improve adherence and quality of life, and to prevent, improve, or resolve some of the secondary effects of ART.

The reasons for modifying and simplifying ART are as follows: to reduce the pill burden and frequency of administration (combinations are now available that can be administered once daily), eliminate dietary restrictions, improve current or potential toxicity, reduce the risk of interactions and take advantage of new formulations, new indications, or new drugs.

Given its advantages, simplification of ART has frequently been requested by patients who have achieved virological suppression with a complex regimen, and it has been the object of a recent review by GESIDA.120 This strategy began to be used with the appearance of the NNs, simpler drugs, with fewer secondary effects and an efficacy similar to that of the PIs available at the time. Most simplification studies have been carried out starting with regimens containing unboosted PIs. The use of low-dose RTV as a booster of other PIs, the new formulations of older PIs such as SQV and the new generations of PI such as LPV, ATV and FPV, have enabled us to design PI-containing regimens without the PI. Therefore, simplification starting with these regimens may not be as necessary as before.

ART can be simplified by reducing the number of drugs, pills, or doses, all of which has been shown to improve adherence.117

Reducing the number of drugs

The first ART simplification studies aimed to reduce the number of drugs in what came to be known as the induction-maintenance strategy. This strategy involved a first induction phase with three or four antiretrovirals followed by a maintenance phase with fewer than three drugs.

These first studies did not manage to maintain virological control by using fewer than three drugs.106,107 Some of the possible reasons for the failure of the maintenance regimens used could be an excessively short induction time (3 to 6 months), a VL limit that was too high to start a maintenance regimen (200 or 500 copies/mL), the inclusion of patients with possible resistance to one of the drugs, or the lower potency of the combination of only two drugs. Therefore, the failure of these studies is probably due more to their design than to the fact that the strategy itself was erroneous.

Recently, the strategy of simplifying to monotherapy with LPV/r has begun to be studied, after having achieved virological suppression during an induction period with triple therapy including this drug.124 This approach is justified by the potency of the drug and by the apparent absence of resistance to it when the regimens containing it fail. Therefore, eventual rescue of a failure would not be compromised. The results of a randomized clinical trial including 188 patients followed up for 48 weeks shows the viability of this strategy, although more follow-up and experience is necessary before it can be recommended in clinical practice.200

This same strategy is being explored with ATV/r, although the only study available at the moment is a pilot study with a limited number of patients and no control arm.201

Reduction of pill burden and/or number of doses

Pill burden and/or number of doses can usually be reduced when a drug from another group substitutes the PI from the previous regimen. In this strategy, which has been widely studied, three drugs have been evaluated for substituting the PI: EFV, NVP and ABC. There is evidence that the stable virological suppression and immunological improvement achieved with a regimen including one or several PI are adequately maintained or even improve when the PI is switched to EFV, NVP or ABC.

The advantages of this strategy include an improvement in quality of life and adherence, and in some cases, a reduction in secondary effects, especially those related to the lipid profile. The improvement in lipid profile has been observed more intensely in the different studies in which simplification has been to NVP or with abacavir.202

In patients with no previous failure of NA, there are no notable differences in efficacy between the three drugs used when substituting the PI. In patients with a previous failure on NAs or previous suboptimal therapy, a greater number of virological failures has been observed due to accumulation of mutations of resistance to NAs, a fact that is most observed in the group of patients who simplify to abacavir.

In those cases where the wish is to maintain the PI, it is possible to simplify to unboosted ATV or boosted ATV if it is combined with TDF.203

Recommendations

- In patients with no previous failure with NAs or previous therapy with NAs in monotherapy or bitherapy, treat...
ment can be simplified indiscriminately to EFV, NVP, ABC or ATV (level A).

- It is not recommended to simplify to ABC when there are previous suboptimal treatments with NAs (level A). Simplification to ABC combined with TDF and 3TC or to TDF and ddI is contraindicated (level B).

- In patients with an undetectable VL in their first regimen, it is possible to simplify to a QD regimen consisting of ddI + TFC + EFV, TDF + 3TC + EFV and, probably, to ddI + TFC + EFV (level A).

- Other possible combinations should be made in the framework of clinical trials and not, for the moment, in habitual clinical practice (level C).

Conclusion

This document has updated the latest data from publications or communications at scientific meetings on antiretroviral therapy. Given the characteristics of the document, the content has been reduced substantially. Previous recommendations examined integral antiretroviral therapy in the seropositive patient with or without other concomitant conditions, pregnancy, etc., in addition to drug adverse effects, pharmacokinetic interactions, and post-exposure prophylaxis. This information can be found in a more extensive document on the web pages of GESIDA and PNS.

Recomendations of GESIDA/Spanish AIDS Plan on antiretroviral therapy

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Acknowledgments

GESIDA and the PNS would like to thank the following people, whose comments on the preliminary version of this document posted on the web pages have improved and enriched the text. Dr. Manuel Cozar, Dr. Manuel Ortíz, Dr. Eusebio Pérez, Dr. Vicente Rivadulla, Dr. Daniel Sanz, Dr. Javier Saura, Dr. Belén Varela.

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