

Recommendations of GESIDA/Spanish AIDS Plan on antiretroviral therapy in adults infected by the human immunodeficiency virus (Updated January 2007)

Expert Committee of GESIDA and the National AIDS Plan



Committee:

Coordinators:

José López Aldeguer, Federico Pulido, Rosa Polo

Members (in alphabetical order):

Antonio Antela, Jose R. Arribas, Julio Arrizabalaga, Juan Berenguer, Bonaventura Clotet, M^a José Galindo, José M^a Gatell, Juan González García, José Antonio Iribarren, José María Kindelán, Pablo Labarga, Fernando Lozano, Esteban Martínez, Celia Miralles, José M^a Miró Meda, Santiago Moreno, Daniel Podzamczar, Joaquín Portilla, Esteban Ribera, Melcior Riera, Antonio Rivero, Rafael Rubio, Jesús Santos, Juan Miguel Santamaría, Jesús Sanz, Ferran Segura, Vicente Soriano, Montserrat Tuset, Pompeyo Viciano

Summary

Objective: To update antiretroviral therapy (ART) recommendations for adult patients infected with the human immunodeficiency virus (HIV-1).

Methods: To formulate these recommendations, a committee composed of members of the Grupo de Estudio de Sida (GESIDA; AIDS Study Group) and the Plan Nacional sobre el Sida (PNS; Spanish National AIDS Plan) reviewed the advances in 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 of these situations.

Results: Currently, the treatment of choice for chronic HIV-1 infection is the combination of three drugs, including 2 nucleosides or nucleotide analogs (NA) plus 1 non-nucleoside (NN) 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 based on CD4+ lymphocyte counts per microliter (μl) 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 the CD4+ count remains 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 objective of ART is to achieve an undetectable viral load. Therapeutic options are limited with the development of cross-resistance. Genotyping studies are useful in these cases. More information regarding the committee recommendations for adherence, toxicity, treatment during pregnancy, hepatitis B or C virus co-infections and post-exposure prophylaxis is available 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 mean that therapy is increasingly tailored to individual needs.

1. 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 drugs.¹⁻³

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 healthcare 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 2004⁴ 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 by the 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.

1. 1. 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.

1. 2. 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 survival.⁵⁻¹⁴
2. Adherence to ART plays a crucial role in virological response and its duration.¹⁵
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 ART.^{1,3,4,16}
4. Treatment aims to reduce VL to below the limits of detection set by commercially available methods, wherever possible by ultrasensitive methods (<20 to <50 copies/ml), and for as long as possible.^{1,3,4,17}
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.^{16,18}
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,^{1,3,4,20} 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.²¹

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

2. 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.

2.1. 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.

2.2. 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.^{16,18,24,25} The proliferative response to memory antigens and mitogens is restored and this allows prophylaxis of opportunistic infections to be suspended.²⁴⁻²⁶

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 general, cell kinetics studies show that during the first year there should be an increase of at least 50–100 CD4 lymphocytes/ μ l.²⁷ 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 (\pm 20%) means that the number of CD4 lymphocytes must always be measured before taking any decisions concerning therapy.²⁸⁻³⁰

2.3. 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 log₁₀/ml) after initiating ART and the nadir reached at 4–8 weeks correlates with the duration of the response.³¹⁻³³ In naïve 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.^{36,37} 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.³² Although some studies show that there is a greater risk of failure in patients who experience frequent transitory rebounds in VL (blips),³⁸ most do not show a great incidence of virological failure in patients with a complete virological response.³⁹⁻⁴² 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 (decrease $\geq 1 \log_{10}/\text{ml}$), 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.⁴³

2.4. Resistance of HIV-1 to antiretroviral drugs

The appearance of viral strains with resistance variants can be detected using genotypic or phenotypic techniques.⁴⁴ 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 to 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.⁴⁴ Finally, resistance tests should be performed during ART⁴⁵ 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,^{46–48} 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.^{49,50} One multicenter study of recently infected patients found a preva-

lence of 14% of strains containing resistance mutations⁵¹ and the researchers verified its relationship with the prevalence of patients with a detectable VL.⁵² One study from the U.S. used a similar model to determine the clinical benefit and cost-efficacy relationship of genotypic resistance testing on all chronically infected naïve patients using a simulated model of HIV-1 (*The Cost-Effectiveness of Preventing AIDS Complications model*), based on the parameters of the natural history of the infection obtained from the MACS cohort. The authors conclude that the genotypic study is cost-effective in these patients and should therefore form part of their health care.^{53,54}

In pregnant women, there is a clear relationship between VL and the risk of vertical transmission.⁵⁵ This risk has also been observed to be 5 times greater if there are zidovudine (ZDV)-resistant strains, and this factor is independent of VL.⁵⁶

Recommendations. Resistance studies are helpful, as they allow drugs to be used better⁴⁴ (**level A**). There is also a public health benefit for the community, since better use of ART will probably reduce the appearance potentially transmissible resistance (**level C**).

At present, genotypic testing to detect resistance is indicated in health-care practice⁵⁷ in the situations set out in Table 1.

3. ACUTE HIV-1 INFECTION

HIV-1 primary infection is symptomatic in more than half of all cases, although it could go unnoticed, as its symptoms are similar to those of common virosis, and this usually delays diagnosis.⁵⁷⁻⁶¹ Therefore, this should be suspected in all seronegative patients with HIV-1 risk practices and compatible symptoms. As there are still no antibodies at this stage (window period), VL should

be determined or, if this is not possible, antigen p24 should be determined. The sensitivity and specificity of VL are 100% and 97% respectively;⁶² the few false positives 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.⁶² In general, these patients' VL is very high, often more than 6 log₁₀/ml. Clinical manifestations usually appear about 2 weeks after infection and with current ELISA testing, seroconversion can be detected 1-2 weeks later.⁶³ By contrast, HIV-1 RNA can be detected in plasma the week before the onset of symptoms. 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.⁶¹ 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.¹⁴³ Acute infection (diagnosed before seroconversion) should not be confused with recent infection (less than six months' duration).⁶¹

At present, initiating ART during acute infection is somewhat controversial,⁶⁴ 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.⁶⁴ Recent cohort studies^{65,66} 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.⁶⁵⁻⁶⁷

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 baseline ART regimens as for chronic infection 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**).

4. CHRONIC HIV-1 INFECTION

4.1. 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.

4.1.1. 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.^{10,13,18} These spectacular re-

sults, 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.^{15,44}

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/ μ l.

Data from observational studies⁶⁸⁻⁷⁹ suggest that:

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

those who start therapy when the CD4+ lymphocyte figure is higher than 350 cells/ μ l, 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/ μ l (especially if the CD4 percentage is below 15%) than in those who start therapy with more than 350 cells/ μ l.

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)⁸⁰ 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/ μ l and on VL (Table 2):

1. Patients with a CD4+ count of < 200 cells/ μ l should initiate ART (**level A**).
2. Patients with a CD4+ count of between 200 and 350 cells/ μ l 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/ μ l than to 200 cells/ μ l. Nevertheless, therapy could be delayed in those patients whose CD4+ lymphocytes remain stable at approximately 350 cells/ μ l and whose VL is low (more or less below 20,000 copies/ml).
3. Patients with a CD4+ of > 350 cells/ μ l 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.¹⁵

4.1.2. 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).¹⁻⁴ Most of these combinations allow a VL of <50 copies/ml to be reached at 48 weeks in 60-70% of cases.⁸¹

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 also 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 pharmacokinetic 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 the cost of ARD when setting up preferred treatment schedules.

With respect to the different combinations of ART, this committee wishes to make several points. **First:** most experience in patients with advanced immunosuppression (CD4+ lymphocyte count <100 cells/ μ l) is with combinations of NAs with lopinavir/ritonavir (LPV/r) or efavirenz (EFV).⁸²⁻⁸⁶ **Second:** regimens composed of 3 NAs are less efficacious than regimens composed of 2 NAs + 1 NN⁸⁷ and there are data indicating that they are less efficacious than 2 NAs + 1 PI in patients with a very high VL.²⁸⁸⁻⁸⁹ **Third:** there is little clinical experience with the combination of ARD from the three families (NA, NN and PI); although this ART can be very potent, its complexity, toxicity and limited future therapeutic options in the case of failure mean that it cannot be recommended as initial therapy.¹⁻⁴ The same is true for regimens including only two PIs.¹⁻⁴ **Fourth:** the combination of an NN and a PI has proven to be as efficacious as triple therapy with PIs in a recent study,⁸² although this was not the case in others,⁹⁰ and it could even be more toxic in its impact on lipid metabolism.^{91,92} **Fifth:** fusion inhibitors (FI), such as enfuvirtide (T-20), are not used in initial therapy and should be kept for 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 regimen.⁹³⁻⁹⁵

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

alternative 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 regimens based on a boosted protease inhibitor (PI/r) with low-dose ritonavir (RTV): 1) High efficacy proven in numerous clinical trials, 2) Low pill burden (soon one pill) makes them easier to use, 3) Fewer serious pharmacokinetic 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 best indicated in treatment-naïve patients. The use of NNs in rescue regimens is compromised by a reduction in the activity of the other components of the regimen.

The main advantage of PI/r is their high genetic barrier 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 ART.⁹⁶

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

In Spain, 7 NAs are commercialized: ZDV, didanosine (ddI), zalcitabine (ddC), stavudine (d4T), lamivudine (3TC), emtricitabine (FTC) and abacavir (ABC). One NtA, tenofovir DF (TDF), is also commercialized. For practical purposes in these guidelines, the abbreviation NA includes TDF. ddC will shortly be taken off the market.

The combination of two NAs is included in most triple or quadruple therapies.¹⁻⁴ The committee considers that the combinations of choice are TDF + FTC, ABC + 3TC and ZDV + 3TC, since their tolerance and efficacy have proven acceptable in several clinical

trials. Furthermore, available data show that either FTC or 3TC can generally be administered. It must be stressed that these three combinations present very different toxicity profiles. ZDV has a greater risk of causing lipoatrophy than TDF.⁹⁷⁻⁹⁸ Between 5% and 8% of patients treated with ABC develop a hypersensitivity reaction whose incidence will probably decrease with the genotyping of HLA-B*5701. Many reports of isolated cases and some cohort studies reveal deterioration in the renal function of patients exposed to TDF, which is generally associated with other nephrotoxic factors, although this has not been proven in clinical trials.

Combinations with ZDV + ddI and ddI + 3TC may be an alternative, although information is scarce. The only data on the combination ddI + FTC come from a clinical trial,⁹⁹ 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 alternative regimen today due to its greater toxicity. The combination 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 pancreatitis or hepatic steatosis.¹⁰⁰ The combination TDF + ddI must not be administered at all due to its greater toxicity and lower efficacy.¹⁰¹⁻¹⁰⁵ The committee considers that ZCV + d4T should not be administered because of antagonism and that ddC should not be administered with any NA because of toxicity associated with ddC.¹⁻⁴ Neither is it recommended to use FTC with 3TC, since they have a similar resistance profile and probably have few associated clinical benefits.

In any case, the final choice of combination of NA must be on an individual

basis taking into account the characteristics of the drug, clinical situation, and patient preferences. Easy regimens can facilitate adherence. These include 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 combinations probably improve adherence, although it is arguable whether this advantage is clinically relevant.¹⁰⁶

The combination ZDV + 3TC is a simple, efficacious regimen with wide clinical experience. Its cost, in coformulated tablets, is lower than that of coformulations of TDF + FTC or ABC + 3TC. The combination ABC + 3TC is equivalent to ZDV + 3TC.¹⁰⁷ There is no clinical trial experience with the combination ABC+3TC with nevirapine (NVP) or with atazanavir (ATV). TDF + 3TC is efficacious in combination with EFV.¹⁰⁸ 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]).¹⁰⁹ The combination TDF + 3TC is more efficacious than AZT + 3TC when associated with EFV, although the difference seems to be due essentially to the lower toxicity of the former in the short term and medium term.⁹⁸ There is no experience with the combination TDF + 3TC (or FTC) plus NVP. In general, it is reasonable to extrapolate the results obtained with 3TC to those obtained with FTC and vice versa (**level C**).

The combination ddI + FTC associated with EFV, is superior to ddI + d4T + EFV.⁹⁹ There is no experience with the combinations ddI + 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 + 3TC.¹⁰⁸ Therefore, the combination d4T + 3TC is considered an alternative regimen. In addition to TDF + 3TC or FTC, ABC + 3TC and ddI + FTC, other combinations of NA could be used in once-daily regimens, although their long-term virological efficacy has not yet been determined (ddI + 3TC).^{99,110}

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 trial⁹⁸ has shown a greater risk of developing lipoatrophy 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 lipoatrophy in patients treated with ZDV or ABC, evidence from other trials^{111,112} suggests that ABC is similar to TDF with regard to the risk of developing lipoatrophy. Other alternatives are ddI + FTC or 3TC, d4T + 3TC and ZDV + ddI. Available data suggest that FTC and 3TC can be used indistinctly (**level C**). The combinations d4T + ddI and TDF + ddI must be avoided due to their toxicity and lower efficacy. The following combinations are not recommended: ZDV + d4T, 3TC + FTC and ddC + any other NA. Prudence is recommended with combinations of NAs and/or NtA 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 PIs.⁸⁸⁻⁸⁹ Therefore, the combination ZDV (or d4T) + 3TC + ABC should only be used in treatment-naïve patients as an alternative to a regimen with NN or with 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 + ddI + ABC as initial therapy.¹¹³ Furthermore, combinations of 3 NAs that include ABC + 3TC + TDF or ddI + 3TC + TDF should not be used in any patient..¹¹⁴⁻¹¹⁶

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 + ddI + ABC as initial therapy (**level A**). The committee also recommends not using at any time 3-NA regimens containing abacavir + 3TC + TDF or ddI + 3TC + TDF (**level A**). There is not enough experience to make recommendations with other combinations of 3 NAs and/or NtAs.

4.1.4. 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 pregnancy.¹¹⁷ 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 regimen.¹¹⁸ 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 family.⁴⁴

To date, it has been shown that regimens with EFV or NVP are more efficacious than those with 3 NAs.^{87,88} Furthermore, several studies have shown that a regimen with EFV is more efficacious than a regimen with some PIs (indinavir [IDV],⁹⁰ nelfinavir [NFV],¹¹⁹ saquinavir boosted with ritonavir [SQV/r],¹²⁰ amprenavir boosted with ritonavir [APV/r],¹¹⁴ LPV/r⁸²). 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 conclusions.¹¹⁸

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, concentration disorders and/or somnolence. 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 in-

crease 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 continued at frequent 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+ lymphocyte count of >250 cells/ μ l compared with those who have a count of < 250 cells/ μ l (11% vs. 0.9%). Similarly, an increased risk has been reported in men with a CD4+ lymphocyte count > 400 cells/ μ l 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 prefers 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/ μ l or in men with a count of >400 cells/ μ l. NVP should be used with extreme caution in patients affected by hepatotropic viruses.

4.1.5. Protease inhibitors

In Spain, 8 PI are commercialized: saquinavir (SQV), indinavir (IDV), ritonavir (RTV), nelfinavir (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 experience.^{6,8} 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 prodrug 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 rescue 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 and 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 C_{min}/CI₅₀ 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 study.^{35,121} Once-daily LPV/r (6 capsules) has proven to be as efficacious as administration every 12 hours, although with a greater frequency of diarrhea.¹⁰⁹ 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 intake.¹²² 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, studies¹²³⁻¹³⁰ 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 consid-

ers 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**).

4.2. 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.

4.2.1. 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.^{27,131,132} 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 (PI/r), 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.¹³³⁻¹³⁴ The modern ART era shows a generalized preference for very simple regimens combining non-thymidine NAs and NNs or PI/r, 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.¹³⁵

4.2.1.1. 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.¹³⁶⁻¹³⁸

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 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.^{138,140}

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.^{40,141}

4.2.2. 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 transitory 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,^{39,41,42,142} and can appear in combined therapy with NNs or PIs.¹⁴³ Nevertheless, the study with the greatest number of patients, carried out in the Frankfurt and Swiss cohorts, found that 704 of 2055 patients with efficacious ART developed blips (490 with one episode and 155 with two episodes). In patients who suffered a rebound, the risk of virological failure was two times greater than in those patients who maintained a suppressed VL, whereas in those who had two consecutive determinations of VL of between 50 and 500 copies of RNA/ml, the risk of failure increased more than five-fold.³⁸ The discrepant results of these studies may be due to the number of patients included, length of follow-up, the periodicity of the VL determinations, or to

differences in the study populations. These same reasons could explain why, in some studies, there is a genetic evolution of HIV-1 and selection of resistance to antiretroviral drugs during blips.^{41,142}

Immunological failure (see Section 2) is usually preceded by virological failure. Occasionally, some patients with undetectable 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 + ddI. Treatment with IL-2 should be considered.^{144,145}

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 processes¹⁴⁶ 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.

4.2.3. 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 the failed 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**).

4.2.4 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 resuppression 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).

4.2.4.1. 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, 3TC 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.^{135,148,149} In these cases, two thymidine analogs (ZDV and d4T), NNs and PIs remain active. Furthermore, it is well known that patients with previous failures to NAs are hypersusceptible to EFV, 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.

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

NNs, especially EFV, are the most widely used drugs in initial ART. A single mutation (e.g., 103N) 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 (depend-

ing 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.

4.2.4.3. 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 PI/r 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 PIs (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 num-

ber of patients.^{159,160} Furthermore, when virological failure is detected in a patient receiving a regimen containing boosted PIs, mutations may not be detected in the protease gene, although they may be detected in the reverse transcriptase gene.^{35,161}

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.^{1,162}

Another simple and efficacious regimen consists of a combination of 2 new NAs and 1 NNs. The lack of cross-resistance between PIs and NNs, as well as hypersusceptibility to NNs in patients with a certain degree of resistance to NAs¹⁵⁰ speak 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 NAs and not exposed to NNs, the inclusion of an NN in the new therapy improves the virological response.¹⁶³ If this option is chosen, the 2 NAs 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 PI/r. This option would be limited to situations that do not involve mutations of resistance to the new therapy (**level C**).
- One or two new NAs (chosen depending on the results of the resis-

tance test) with a second PI/r 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**). NAs and PIs should be chosen according to the results of the resistance test.

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

4.2.5.1. Definition:

Treatment after 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: NAs, NNs and PIs.

4.2.5.2. 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 resuppression 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.¹⁶⁴ Furthermore, directly observed treatment strategies, which are currently available thanks to the large number of QD regimens, may prove useful in specific populations.^{165,166}
- **Resistance testing.** A genotypic or phenotypic resistance test with each virological failure can optimize the new treatment, increase its efficacy, and improve prognosis.¹⁶⁷
- **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 PI/r.¹⁶⁸
- **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,¹⁶⁹ e.g., with 2 boosted PIs, and may require dose adjustment.⁶² It may also be useful if the objective is to increase the PI dose in order to increase its inhibitory quotient.¹⁷⁰

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.

4.2.5.3. 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.

4.2.5.3.1. 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.¹⁷¹ This drug has recently been approved in Spain and is indicated for HIV-1-infected patients who have received several antiretroviral drugs and who are carriers of viral populations that are resistant to various PIs. The approved dose is 500 mg BID in combination with RTV 200 mg BID.

The antiviral efficacy of TPV has been proven in two phase III studies with an identical design: RESIST-1 with 630

patients in North and South America, and RESIST-2 with 876 patients in Europe and Australia.¹⁷²

TPV boosted with low doses of RTV is efficacious for reaching the therapeutic objective marked in this situation, especially if it is associated with T-20. Its main disadvantage is its greater liver and metabolic toxicity than other available PI/r.¹⁷²

Darunavir (TMC114). This PI, which has not yet been approved by the European Agency for the Evaluation of Medicinal Products, but which is available in many Spanish centers through expanded access programs, has been specially designed to be active against HIV-1 strains with mutations in the protease gene.¹⁷³ Two clinical trials (POWER 1 and 2) in phase IIb have evaluated the efficacy and tolerance of different doses of TMC114 boosted with RTV against a comparator boosted PI (CPIr), both combined with other antiretroviral drugs according to a resistance test. The patients included should have been treated previously with NAs, NNs and PIs, and they should have presented at least one primary mutation in the protease gene and a VL of > 1000 copies/ml. We now have the results of 110 patients followed up until week 48; they reveal a greater efficacy of TMC114 against the comparator PI. A VL of < 50 copies/ml was observed in 46% of those who received darunavir compared with 10% of those who received the comparator PI. When T-20 was added, 58% of patients in the TMC114 arm had an undetectable VL compared with 11% in the other arm. The increase in CD4 was 102 compared with 19 cells/ μ l.¹⁷⁴ The proposed dose of TMC114 is 600mg boosted with 100 mg of de RTV every 12h. To date, the efficacy of darunavir as a rescue therapy has not been compared with that of TPV.

Another clinical trial, POWER 3 (with inclusion criteria and baseline characteristics similar to those of POWER 1 and 2) included 327 patients and was designed to extend the safety and tolerability database, although the efficacy of the drug was also measured. The data of this study corroborate the results of POWER 1 and 2 at 48 weeks. All three studies showed that darunavir seems to be well tolerated, the most common adverse effects being nausea and headache. It also seems to show a better hepatic profile than CPIr and a lipid profile similar to that of CPIr.¹⁷⁵

Recently, 11 genotypic mutations have been identified (V11I, V32I, L33F, I47V, I50V, I54L or M, G73S, L76V, I84V, L89V), and they have been associated with reduced sensitivity to TMC114 in more than 9,600 samples from different clinical trials with multi-treated patients. The presence of 3 or more of these mutations at baseline was associated with a lower percentage of patients with an undetectable VL at week 24, although the percentage of patients with an undetectable VL was greater than in the control arm. With only one or two of these baseline mutations, the percentage of patients with a VL <50 copies/ml was 57% and 46%, respectively, in the TMC114/r arm. The presence of 3 of these mutations was associated with a high number of mutations (greater than or equal to 9) in other positions of the protease gene.¹⁷⁶

4.2.5.3.2 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/ μ l. At 24 weeks, the fall in VL was significantly greater in the patients treated with T-20 than in the patients treated with the optimized ART regimen only. T-20 produced an additional fall in VL of $-0.93 \log_{10}$ in the TORO I study and of $-0.78 \log_{10}$ in TORO II ($p < 0.0001$).^{177,178} In the combined analysis of both studies, the fall in VL at week 48 compared with baseline was $-1.48 \log_{10}$ copies/ml for the group that received T-20 compared with $-0.63 \log_{10}$ copies/ml for those who received the optimized therapy only ($p < 0.0001$).¹⁷⁹ 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 \log_{10} 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, 32 and 11 weeks, respectively ($p < 0.0001$).¹⁸⁰ 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 multitreated 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,¹⁸¹ the response at week 12 helps to predict the response to therapy.¹⁸² 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 $\geq 1 \log_{10}$ at week 12, 59.5% (95%CI: 53.8%-65.1%) maintained a VL < 400 copies at weeks

96, and 39.2% (95%CI: 33.6%-44.8%) maintained a VL < 50 copies, compared with 2.6% (95%CI: 0%-6.1%) and 1.3% (95%CI: 0-3.8%), 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.^{177,178}

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.

4.2.5.3.3. 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 FPV 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 (400/100mg BID) plus ATV (300 mg QD) in 16 patients with few therapeutic options.¹⁸⁷ This combination achieved high plasma concentrations of both PIs, 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.

4.2.5.4. 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 experiencing virological failure. In this situation, TPV/r or TMC114/r plus T-20 plus recycled antiretroviral drugs are the regimens that achieve the best results (**level A**).
- The new ART regimen should be comfortable, well tolerated, and as minimally toxic as possible. Adherence to therapy should be guaran-

teed before starting rescue therapy (**nivel C**).

4.2.6. 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/ μ l or a fall of at least 0.5 log₁₀ in VL is considered successful, 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.^{132,188,189} 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.¹⁹⁰

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^{191,192}. The possibility must be considered of referring these patients to a center with experimental drugs in clinical trials.

4.2.6.1. Therapy with ≥ 5 antiretroviral drugs (“mega-HAART”)

One option for rescue therapy that aims for complete suppression of viral repli-

cation is combination therapy 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.

4.2.6.2. 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.

4.2.6.3. 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 viral strain, either alone or in combination with 1 or 2 NAs that the patient can tolerate without difficulty, thus enabling viral replicatory capacity to be reduced.¹⁹³

4.2.6.4. Introduction of new antiretroviral drugs in advanced clinical trials

The best 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 involves a transitory improvement in the patient’s immunological status.

4.2.6.5. Recommendations in multi-resistant HIV-1 infection

- It is not recommended to interrupt therapy, especially if the CD4⁺ lymphocyte count is ≤ 200–250/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 prognosis. The possibility of referring the patient to a center with experimental drugs should be considered.
- All treatment 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 advis-

able to maintain a suboptimal treatment. In this case, it is also indicated to maintain 3TC or FTC.

4.3. 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.¹⁹⁴ 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 that do not present the problems of complexity and tolerance observed

with first-generation PIs. 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.⁸¹

4.3.1. 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.¹⁹⁵⁻¹⁹⁷ 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.¹⁹⁸ 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.¹⁹⁹ 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 198 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

4.3.2. 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, treatment 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 + FTC + EFV, TDF + 3TC + EFV and, probably, to ddi + 3TC + 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.

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 page have improved and enriched the text: Dr. Manuel Cotarelo, Dr. Manuel Distel, Dr. Pere Domingo, Dr. Ismael

Escobar, Dr. Víctor Gutiérrez Rave, Dr. Hernando Knobel, Dr. Cindy McCoig, Dr. Jaime Locutura, Dr. Juan Carlos López Bernaldo de Quirós, Dr. Josep Mallolas, Dr. Michael Mullen, Dr. Francisco Pascuau, Dr. Maria Jesús Pérez Elías, Dr. José A. Pérez Molina, Dr. Juan A. Pineda, Dr. Pablo Rivas, Dr. Oscar Serrano and Dr. Belén Vendrell.

Table 1. Indications for resistance testing in clinical practice*

A. Naïve patients

Pregnant women
Acute HIV infection
Post-exposure prophylaxis (source case)
Patients about to start ART (if no previous study is available)

B. Experienced patients

In all failures.

* All patients should undergo genotypic resistance testing before initiating antiretroviral therapy. This could be included as part of the initial screening.

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

CD4 lymphocytes	Asymptomatic patients
<200	Always recommend
200-350	Recommend on most occasions *
>350	Defer

* In general, patients with a CD4+ lymphocyte count of between 200 and 350 cells/ μ L should initiate ART, especially if the number of CD4 is below 14%. However, in certain circumstances ART could be deferred: if the CD4+ lymphocyte remains stable at approximately 350 cells/ μ L and viral load is low (<20,000 copies/ μ L).

Table 3. Combinations of antiretroviral therapy in treatment-naïve patients*

POSSIBLE COMBINATIONS	REGIMENS		
PREFERRED REGIMENS	One drug from column A + one from column B + one from column C		
ALTERNATIVE REGIMENS	A ¹	B ¹	C ²
	Tenofovir (TDF) Abacavir (ABC) Zidovudine (AZT)	Lamivudine (3TC) Emtricitabine (FTC)	Efavirenz Lopinavir/r Fosamprenavir/r
	Didanosine (ddI) Stavudine (d4T)		Nevirapine Atazanavir/r** Saquinavir/r Atazanavir** Nelfinavir
REGIMEN FOR WHEN PI OR NN CANNOT BE USED	ABC + 3TC + AZT		
CONTRAINDICATED REGIMENS	Regimens with unboosted SQV Regimens with some combinations of NA (3) ABC + 3TC + TDF ddI + 3TC + TDF d4T + ddI + ABC		

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

1. Available data suggest that 3TC and FTC can be used indiscriminately (level C). The NA combinations of choice as part of initial triple regimens are TDF + FTC (or 3TC), ABC + 3TC (or FTC) or AZT + 3TC (or FTC). 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 + 3TC. The latter combination is efficacious, and there 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 + 3TC with nevirapine, with lopinavir/r or with atazanavir/r). There is no experience with TDF + 3TC in combination with a PI as initial therapy, but there is with TDF + FTC (in combination with lopinavir/r). There is no experience with the combination TDF + 3TC plus nevirapine. The combination d4T + 3TC is efficacious, but alterations in lipid metabolism, lipodystrophy, and peripheral neuropathy mean that it is considered an alternative regimen. The combination 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.
2. 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 + 3TC. It can be administered comfortably (once daily) and seems to have a good lipid profile. It is preferable to use boosted PIs.
3. AZT + d4T, FTC + 3TC, TDF + ddI, ddI + d4T and any combination with ddC.

Consulting the text will make for a better interpretation of the table.

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

Previous regimen	New regimen
3 NAs	2 NAs ^a + NN or PI/r ^{b, c} 1 or 2 NAs ^a + NN + PI/r ^{b, c}
2 NAs + 1 NN	2 NAs ^a + PI/r ^{b, c}
2 NAs + PI or PI/r ^b	2 NAs ^a + 1 NN ^d 2 NAs ^a + PI/r ^{b, c, e} 1 or 2 NAs ^a + 1 NN ^d + PI/r ^{b, c, e}

Abbreviations: NA: nucleoside/nucleotide analog reverse transcriptase inhibitor; NN: non-nucleoside reverse transcriptase inhibitor; PI/r: protease inhibitor boosted with ritonavir.

Notes:

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

^b Administration of a PI/r improves the pharmacokinetics of the PI, reduces the incidence of mutations of resistance to PI, and facilitates adherence.

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

^d In a previous failure with NA in patients naïve for NN, inclusion of an NN (efavirenz) in the new therapy improves the virological response.

^e When a PI/r 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 PI/r can be maintained unless there is intolerance, toxicity or poor adherence.

REFERENCES

1. Panel on Clinical Practices for Treatment of HIV Infection convened by the U.S. Department of Health and Human Services (DHHS). Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents – Oct 10, 2006. <http://AIDSinfo.nih.gov> (Accessed 10.11.2006).
2. Gazzard B. British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy (2005). *HIV Med* 2005; 6 Suppl 2:1-61.
3. Hammer SM, Saag MS, Schechter M, Montaner JS, Schooley RT, Jacobsen DM et al. Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society-USA panel. *JAMA* 2006; 296:827-843.
4. Iribarren JA, Labarga P, Rubio R, Berenguer J, Miro JM, Antela A et al. Recomendaciones de GESIDA/Plan Nacional sobre el Sida respecto al tratamiento antirretroviral en pacientes adultos infectados por el virus de la inmunodeficiencia humana (Octubre 2004). *Enferm Infecc Microbiol Clin* 2004; 22:564-642.
5. Alberdi JC, Lopez-Gay D, Ferreras A, Nieto E. Descenso brusco de la mortalidad por VIH-1/SIDA en la Comunidad de Madrid. *Med Clin (Barc)* 1998; 110:679.
6. Cameron DW, Heath-Chiozzi M, Danner S, Cohen C, Kravcik S, Maurath C et al. Randomised placebo-controlled trial of ritonavir in advanced HIV-1 disease. The Advanced HIV Disease Ritonavir Study Group. *Lancet* 1998; 351:543-549.
7. Fischl MA, Richman DD, Grieco MH, Gottlieb MS, Volberding PA, Laskin OL et al. The efficacy of zidovudine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. *N Engl J Med* 1987; 317:185-191.
8. Hammer SM, Squires KE, Hughes MD, Grimes JM, Demeter LM, Currier JS et al. A controlled trial of two nucleoside analogues plus didanosine in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. *N Engl J Med* 1997; 337:725-733.
9. Hammer SM, Katzenstein DA, Hughes MD, Gundacker H, Schooley RT, Haubrich RH et al. A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500 per cubic millimeter. AIDS Clinical Trials Group Study 175 Study Team. *N Engl J Med* 1996; 335:1081-1090.
10. Mocroft A, Vella S, Benfield TL, Chiesi A, Miller V, Gargalianos P et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. *Lancet* 1998; 352:1725-1730.
11. Mouton Y, Alfandari S, Valette M, Cartier F, Dellamonica P, Humbert G et al. Impact of protease inhibitors on AIDS-defining events and hospitalizations in 10 French AIDS reference centres. Federation National des Centres de Lutte contre le SIDA. *AIDS* 1997; 11:101-105.
12. Palella FJ, Jr., Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998; 338:853-860.
13. Paul S, Gilbert HM, Ziecheck W, Jacobs J, Sepkowitz KA. The impact of potent antiretroviral therapy on the characteristics of hospitalized patients with HIV infection. *AIDS* 1999; 13:415-418.
14. Torres RA, Barr M. Impact of combination therapy for HIV infection on inpatient census. *N Engl J Med* 1997; 336:1531-1532.
15. Knobel H, Escobar I, Polo R, Ortega L, Martin-Conde MT, Casado JL et al. Recomendaciones GESIDA/SEFH/PNS para mejorar la adherencia al tratamiento antirretroviral en el año 2004. *Enferm Infecc Microbiol Clin* 2005; 23:221-231.
16. Kelleher AD, Carr A, Zaunders J, Cooper DA. Alterations in the immune response of human immunodeficiency virus (HIV)-infected subjects treated with an HIV-specific protease inhibitor, ritonavir. *J Infect Dis* 1996; 173:321-329.

17. Tebas P, Henry K, Nease R, Murphy R, Phair J, Powderly WG. Timing of antiretroviral therapy. Use of Markov modeling and decision analysis to evaluate the long-term implications of therapy. *AIDS* 2001; 15:591-599.
18. Autran B, Carcelain G, Li TS, Blanc C, Mathez D, Tubiana R et al. Positive effects of combined antiretroviral therapy on CD4+ T cell homeostasis and function in advanced HIV disease. *Science* 1997; 277:112-6.
19. Carr A, Cooper DA. Adverse effects of antiretroviral therapy. *Lancet* 2000; 356(9239):1423-30.
20. Sepkowitz KA. Effect of HAART on natural history of AIDS-related opportunistic disorders. *Lancet* 1998; 351:228-30.
21. Landon BE, Wilson IB, McInnes K, Landrum MB, Hirschhorn LR, Marsden PV et al. Physician specialization and the quality of care for human immunodeficiency virus infection. *Arch Intern Med* 2005; 165:1133-1139.
22. Jacobson MA, Zegans M, Pavan PR, O'Donnell JJ, Sattler F, Rao N et al. Cytomegalovirus retinitis after initiation of highly active antiretroviral therapy. *Lancet* 1997; 349:1443-5.
23. Michelet C, Arvieux C, Francois C, Besnier JM, Rogez JP, Breux JP et al. Opportunistic infections occurring during highly active antiretroviral treatment. *AIDS* 1998; 12:1815-22.
24. Li TS, Tubiana R, Katlama C, Calvez V, Ait Mohand H, Autran B. Long-lasting recovery in CD4 T-cell function and viral-load reduction after highly active antiretroviral therapy in advanced HIV-1 disease. *Lancet* 1998; 351:1682-6.
25. Kostense S, Raaphorst FM, Notermans DW, Joling J, Hooibrink B, Pakker NG et al. Diversity of the T-cell receptor BV repertoire in HIV-1-infected patients reflects the biphasic CD4+ T-cell repopulation kinetics during highly active antiretroviral therapy. *AIDS* 1998; 12:235-40.
26. Lopez Bernaldo de Quiros JC, Miro JM, Pena JM, Podzamczer D, Alberdi JC, Martinez E et al. A randomized trial of the discontinuation of primary and secondary prophylaxis against *Pneumocystis carinii* pneumonia after highly active antiretroviral therapy in patients with HIV infection. Grupo de Estudio del SIDA 04/98. *N Engl J Med* 2001; 344:159-167.
27. Deeks SG, Hecht FM, Swanson M, Elbeik T, Loftus R, Cohen PT et al. HIV RNA and CD4 cell count response to protease inhibitor therapy in an urban AIDS clinic: response to both initial and salvage therapy. *AIDS* 1999; 13:35-43.
28. Brambilla D, Reichelderfer PS, Bremer JW, Shapiro DE, Hershov RC, KATVEnstein DA et al. The contribution of assay variation and biological variation to the total variability of plasma HIV-1 RNA measurements. The Women Infant Transmission Study Clinics. *Virology Quality Assurance Program*. *AIDS* 1999; 13:2269-79.
29. Sax PE, Boswell SL, White-Guthro M, Hirsch MS. Potential clinical implications of interlaboratory variability in CD4+ T-lymphocyte counts of patients infected with human immunodeficiency virus. *Clin Infect Dis* 1995; 21:1121-5.
30. Lopez A, Caragol I, Candeias J, Villamor N, Echaniz P, Ortuno F et al. Enumeration of CD4(+) T-cells in the peripheral blood of HIV-infected patients: an interlaboratory study of the FAC-SCount system. *Cytometry* 1999; 38:231-237.
31. Kempf DJ, Rode RA, Xu Y, Sun E, Heath-Chiozzi ME, Valdes J et al. The duration of viral suppression during protease inhibitor therapy for HIV-1 infection is predicted by plasma HIV-1 RNA at the nadir. *AIDS* 1998; 12:9-14.
32. Raboud JM, Montaner JS, Conway B, Rae S, Reiss P, Vella S et al. Suppression of plasma viral load below 20 copies/ml is required to achieve a long-term response to therapy. *AIDS* 1998; 12:1619-24.
33. Demeter LM, Hughes MD, Coombs RW, Jackson JB, Grimes JM, Bosch RJ et al. Predictors of virologic and clinical outcomes in HIV-1-infected patients receiving concurrent treatment with indinavir, zidovudine, and lamivudine. AIDS Clinical Trials Group Protocol 320. *Ann Intern Med* 2001; 135:954-64.
34. Huang W, De G, V, Fischl M, Hammer S, Richman D, Havlir D et al. Patterns of plasma human immunodeficiency virus type 1 RNA response to antiretroviral therapy. *J Infect Dis* 2001; 183:1455-1465.

35. Hicks C, King MS, Gulick RM, White Jr AC, Eron Jr JJ, Kessler HA et al. Long-term safety and durable antiretroviral activity of lopinavir/ritonavir in treatment-naive patients: 4 year follow-up study. *AIDS* 2004; 18:775-779.
36. Siliciano RF. Scientific rationale for antiretroviral therapy in 2005: viral reservoirs and resistance evolution. *Top HIV Med* 2005; 13:96-100.
37. Nettles RE, Kieffer TL, Simmons RP, Cofrancesco J, Jr., Moore RD, Gallant JE et al. Genotypic resistance in HIV-1-infected patients with persistently detectable low-level viremia while receiving highly active antiretroviral therapy. *Clin Infect Dis* 2004; 39:1030-1037.
38. Greub G, Cozzi-Lepri A, Ledergerber B, Staszewski S, Perrin L, Miller V et al. Intermittent and sustained low-level HIV viral rebound in patients receiving potent antiretroviral therapy. *AIDS* 2002; 16:1967-9.
39. Havlir DV, Bassett R, Levitan D, Gilbert P, Tebas P, Collier AC et al. Prevalence and predictive value of intermittent viremia with combination hiv therapy. *JAMA* 2001; 286:171-9.
40. Lampe FC, Johnson MA, Lipman M, Loveday C, Youle M, Ransom D et al. Viral breakthrough after suppression with highly active antiretroviral therapy: experience from 233 individuals with viral loads of less than 50 copies/ml followed for up to 4 years. *AIDS* 2003; 17:768-70.
41. Mira JA, Macias J, Nogales C, Fernandez-Rivera J, Garcia-Garcia JA, Ramos A et al. Transient rebounds of low-level viraemia among HIV-infected patients under HAART are not associated with virological or immunological failure. *Antivir Ther* 2002; 7:251-256.
42. Lee PK, Kieffer TL, Siliciano RF, Nettles RE. HIV-1 viral load blips are of limited clinical significance. *J Antimicrob Chemother* 2006; 57:803-805.
43. Saag MS, Holodniy M, Kuritzkes DR, O'Brien WA, Coombs R, Poscher ME et al. HIV viral load markers in clinical practice. *Nat Med* 1996; 2:625-629.
44. Hirsch MS, Brun-Vezinet F, Clotet B, Conway B, Kuritzkes DR, D'Aquila RT et al. Antiretroviral drug resistance testing in adults infected with human immunodeficiency virus type 1: 2003 recommendations of an International AIDS Society-USA Panel. *Clin Infect Dis* 2003; 37:113-128.
45. Devereux HL, Youle M, Johnson MA, Loveday C. Rapid decline in detectability of HIV-1 drug resistance mutations after stopping therapy. *AIDS* 1999; 13:123-7.
46. Novak RM, Chen L, MacArthur RD, Baxter JD, Huppler HK, Peng G et al. Prevalence of antiretroviral drug resistance mutations in chronically HIV-infected, treatment-naive patients: implications for routine resistance screening before initiation of antiretroviral therapy. *Clin Infect Dis* 2005; 40:468-474.
47. Wensing AM, Van de Vijver DA, Angarano G, Asjo B, Balotta C, Boeri E et al. Prevalence of drug-resistant HIV-1 variants in untreated individuals in Europe: implications for clinical management. *J Infect Dis* 2005; 192:958-966.
48. Cane P, Chrystie I, Dunn D, Evans B, Geretti AM, Green H et al. Time trends in primary resistance to HIV drugs in the United Kingdom: multicentre observational study. *BMJ* 2005; 331:1368.
49. Gomez-Cano M, Rubio A, Puig T, Perez-Olmeda M, Ruiz L, Soriano V et al. Prevalence of genotypic resistance to nucleoside analogues in antiretroviral-naive and antiretroviral-experienced HIV-infected patients in Spain. *AIDS* 1998; 12:1015-20.
50. Puig T, Perez-Olmeda M, Rubio A, Ruiz L, Briones C, Franco JM et al. Prevalence of genotypic resistance to nucleoside analogues and protease inhibitors in Spain. The ERASE-2 Study Group. *AIDS* 2000; 14:727-32.
51. de Mendoza C, Rodriguez C, Colomina J, Tuset C, Garcia F, Eiros JM et al. Resistance to non-nucleoside reverse-transcriptase inhibitors and prevalence of HIV type 1 non-B subtypes are increasing among persons with recent infection in Spain. *Clin Infect Dis* 2005; 41:1350-1354.
52. de Mendoza C, Rodriguez C, Eiros JM, Colomina J, Garcia F, Leiva P et al. Antiretroviral recommendations may influence the rate of transmission of drug-resistant HIV type 1. *Clin Infect Dis* 2005; 41:227-232.

53. Sax PE, Islam R, Walensky RP, Losina E, Weinstein MC, Goldie SJ et al. Should resistance testing be performed for treatment-naive HIV-infected patients? A cost-effectiveness analysis. *Clin Infect Dis* 2005; 41:1316-1323.
54. Hecht FM, Grant RM. Resistance testing in drug-naive HIV-infected patients: is it time? *Clin Infect Dis* 2005; 41:1324-1325.
55. Mofenson LM, Lambert JS, Stiehm ER, Bethel J, Meyer WA3, Whitehouse J et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. *N Engl J Med* 1999; 341:385-93.
56. Welles SL, Pitt J, Colgrove R, McIntosh K, Chung PH, Colson A et al. HIV-1 genotypic zidovudine drug resistance and the risk of maternal--infant transmission in the women and infants transmission study. The Women and Infants Transmission Study Group. *AIDS* 2000; 14:263-71.
57. Stekler J, Collier A. Treatment of Primary HIV. *Curr Infect Dis Rep* 2002; 4:81-87.
58. Pilcher CD, Eron JJ, Jr., Galvin S, Gay C, Cohen MS. Acute HIV revisited: new opportunities for treatment and prevention. *J Clin Invest* 2004; 113:937-945.
59. Kassutto S, Rosenberg E. Primary HIV Type 1 Infection. *Clin Infect Dis* 2004; 38:1452-1458.
60. Weintrob AC, Giner J, Menezes P, Patrick E, Benjamin DK, Jr., Lennox J et al. Infrequent diagnosis of primary human immunodeficiency virus infection: missed opportunities in acute care settings. *Arch Intern Med* 2003; 163:2097-2100.
61. Miro JM, Sued O, Plana M, Pumarola T, Gallart T. Avances en el diagnóstico y tratamiento de la infección aguda por el VIH-1. *Enferm Infecc Microbiol Clin* 2004; 22:643-659.
62. Daar ES, Little S, Pitt J, Santangelo J, Ho P, Harawa N et al. Diagnosis of primary HIV-1 infection. Los Angeles County Primary HIV Infection Recruitment Network. *Ann Intern Med* 2001; 134:25-9.
63. Lindback S, Thorstensson R, Karlsson AC, von Sydow M, Flamholz L, Blaxhult A et al. Diagnosis of primary HIV-1 infection and duration of follow-up after HIV exposure. Karolinska Institute Primary HIV Infection Study Group. *AIDS* 2000; 14:2333-2339.
64. Smith DE, Walker BD, Cooper DA, Rosenberg ES, Kaldor JM. Is antiretroviral treatment of primary HIV infection clinically justified on the basis of current evidence? *AIDS* 2004; 18:709-718.
65. Voirin N, Smith D, Routy JP, Legault M, Baratin D, Trepo C et al. Effect of treatment during versus after acute retroviral syndrome on HIV viral load and CD4 cell counts within 3 years of infection. 11th Conference on Retrovirus and Opportunistic Infections, San Francisco, February 8--11, 2004 [Abstract 23]
66. Kassutto S, Maghsoudi K, Johnston MN, Robbins GK, Burgett NC, Sax PE et al. Longitudinal analysis of clinical markers following antiretroviral therapy initiated during acute or early HIV type 1 infection. *Clin Infect Dis* 2006; 42:1024-1031.
67. Sued O, Miro JM, Alquezar A, Claramonte X, Garcia F, Plana M et al. Primary human immunodeficiency virus type 1 infection: clinical, virological and immunological characteristics of 75 patients (1997-2003). *Enferm Infecc Microbiol Clin* 2006; 24:238-244.
68. Phair JP, Mellors JW, Detels R, Margolick JB, Munoz A. Virologic and immunologic values allowing safe deferral of antiretroviral therapy. *AIDS* 2002; 16:2455-2459.
69. Cozzi Lepri A, Phillips NA, d'Arminio Monforte A, Castelli F, Antinori A, De Luca A et al. When to start highly active antiretroviral therapy in chronically HIV-infected patients: evidence from the ICONA study. *AIDS* 2001; 15:983-90.
70. Phillips NA, Staszewski S, Weber R, Kirk O, Francioli P, Miller V et al. HIV viral load response to antiretroviral therapy according to the baseline CD4 cell count and viral load. *JAMA* 2001; 286:2560-7.
71. Wood E, Hogg RS, Yip B, Moore D, Harrigan PR, Montaner JS. Impact of baseline viral load and adherence on survival of HIV-infected adults with baseline CD4 cell counts > or = 200 cells/microl. *AIDS* 2006; 20:1117-1123.

72. Hogg RS, Yip B, Chan KJ, Wood E, Craib KJ, O'Shaughnessy MV et al. Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. *JAMA* 2001; 286:2568-77.
73. Wood E, Hogg RS, Yip B, Quercia R, Harrigan PR, O'Shaughnessy MV et al. Higher baseline levels of plasma human immunodeficiency virus type 1 RNA are associated with increased mortality after initiation of triple-drug antiretroviral therapy. *J Infect Dis* 2003; 188:1421-1425.
74. Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JS. Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4+ cell count is 0.200 to 0.350 x 10(9) cells/L. *Ann Intern Med* 2003; 139:810-816.
75. Kaplan JE, Hanson DL, Cohn DL, Karon J, Buskin S, Thompson M et al. When to begin highly active antiretroviral therapy? Evidence supporting initiation of therapy at CD4+ lymphocyte counts <350 cells/microL. *Clin Infect Dis* 2003; 37:951-958.
76. Sterling TR, Chaisson RE, Moore RD. HIV-1 RNA, CD4 T-lymphocytes, and clinical response to highly active antiretroviral therapy. *AIDS* 2001; 15:2251-7.
77. Keruly J, Moore R. Increases in CD4 cell count to 5 years in persons with sustained virologic suppression. 13th Conference on Retrovirus and Opportunistic Infection, Denver, February 5-8, 2006 (Abstract 529)
78. Sterne J, May M, Costagliola D, Egger M, Hogg R, d'Arminio Monforte A et al. Estimating the optimum CD4 threshold for starting HAART in ART-naïve HIV-infected individuals. 13th Conference on Retrovirus and Opportunistic Infection, Denver, February 5-8, 2006 (Abstract 525)
79. Moore DM, Hogg RS, Yip B, Craib K, Wood E, Montaner JS. CD4 percentage is an independent predictor of survival in patients starting antiretroviral therapy with absolute CD4 cell counts between 200 and 350 cells/microL. *HIV Med* 2006; 7:383-388.
80. Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep* 1992; 41(RR-17):1-19.
81. Bartlett JA, DeMasi R, Quinn J, Moxham C, Rousseau F. Overview of the effectiveness of triple combination therapy in antiretroviral-naïve HIV-1 infected adults. *AIDS* 2001; 15:1369-1377.
82. Riddler SA, Haubrich R, DiRienzo G, Peeples L, Powderly WG, Klingman KL et al. A prospective, randomized, Phase III trial of NRTI-, PI-, and NNRTI-sparing regimens for initial treatment of HIV-1 infection - ACTG 5142. XVI International AIDS Conference, Toronto, Canada, 2006 Abstract THLB 0204
83. King MS, Bernstein BM, Walmsley SL, Sherer R, Feinberg J, Sanne I et al. Baseline HIV-1 RNA level and CD4 cell count predict time to loss of virologic response to nelfinavir, but not lopinavir/ritonavir, in antiretroviral therapy-naïve patients. *J Infect Dis* 2004; 190:280-284.
84. Pulido F, Arribas JR, Miro JM, Costa MA, González J, Rubio R et al. Clinical, virologic, and immunologic response to efavirenz or protease inhibitor based highly active antiretroviral therapy in a cohort of antiretroviral-naïve patients with advanced HIV infection (EfaVIP 2 Study). *J Acquir Immune Defic Syndr* 2004; 35:343-350.
85. Miro JM, Pich J, Plana M, Domingo P, Podzamczar D, Arribas JR et al. Immunological reconstitution in severely immunosuppressed antiretroviral-naïve patients (<100 CD4+ cells/mm3) using a non-nucleoside reverse transcriptase inhibitor- or a boosted protease inhibitor-based antiretroviral therapy regimen: 96-week results (the Advanz trial). 10th European AIDS Conference. November 17-20, 2005. Dublin. Abstract PS1/4.
86. Ribaldo H, Kuritzkes DR, Lalama C, Schouten J, Schackman B, Gulik R. Efavirenz-based regimens are potent in treatment-naïve subjects across a wide range of pre-treatment HIV-1 RNA and CD4 cell counts: 3-year results from ACTG 5095. XVI International AIDS Conference; August 13-18, 2006; Toronto, Ontario, Canada. Abstract THLB0211.
87. Gulick RM, Ribaldo HJ, Shikuma CM, Lustgarten S, Squires KE, Meyer III WA et al. Triple-Nucleoside Regimens versus Efavirenz-Containing Regimens for the Initial Treatment of HIV-1 Infection. *N Engl J Med* 2004; 350:1850-1861.

88. van Leeuwen R, Katlama C, Murphy RL, Squires K, Gatell J, Horban A et al. A randomized trial to study first-line combination therapy with or without a protease inhibitor in HIV-1-infected patients. *AIDS* 2003; 17:987-999.
89. Staszewski S, Keiser P, Montaner J, Raffi F, Gathe J, Brotas V et al. Abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine in antiretroviral-naive HIV-infected adults: A randomized equivalence trial. *JAMA* 2001; 285:1155-63.
90. Staszewski S, Morales-Ramirez J, Tashima KT, Rachlis A, Skiest D, Stanford J et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. *N Engl J Med* 1999; 341:1865-73.
91. Duvivier C, Ghosn J, Assoumou L, Soulie C, Peytavin G, Calvez V et al. Lower rate of virological suppression in naive patients initiating HAART with NRTI-sparing regimen compared to standard NRTI-containing regimen: results from Hippocampe – ANRS 121 Trial. 10th European AIDS Conference; November 17-20, 2005; Dublin, Ireland. Abstract PS1/3.
92. Fischl MA, Bassett R, Collier A, Mukherjee L, Demeter L, Tebas P et al. Randomized, controlled trial of lopinavir/ritonavir + efavirenz vs efavirenz + 2 nucleoside reverse transcriptase inhibitors following a first suppressive 3- or 4-drug regimen in advanced HIV disease. 12th Conference on Retroviruses and Opportunistic Infections, Boston, 2005 Abstract 162.
93. Markowitz M, Hill-Zabala C, Lang J, DeJesus E, Liao Q, Lanier ER et al. Induction with abacavir/lamivudine/zidovudine plus efavirenz for 48 weeks followed by 48-week maintenance with abacavir/lamivudine/zidovudine alone in antiretroviral-naive HIV-1-infected patients. *J Acquir Immune Defic Syndr* 2005; 39:257-264.
94. Shafer RW, Smeaton MS, Robbins GK, De Gruttola V, Snyder SW, D' Aquila RT et al. Comparison of four-drug regimens and pairs of sequential three-drugs regimens as initial therapy for HIV-1 infection. *N Engl J Med* 2003; 349:2304-2315.
95. Gulick RM, Ribaldo HJ, Shikuma CM, Lalama C, Schackman BR, Meyer WA, III et al. Three- vs four-drug antiretroviral regimens for the initial treatment of HIV-1 infection: a randomized controlled trial. *JAMA* 2006; 296:769-781.
96. Phillips NA, Dunn D, Sabin C, Pozniak A, Matthias R, Geretti AM, et al. Long term probability of detection of HIV-1 drug resistance after starting antiretroviral therapy in routine clinical practice. *AIDS* 2005;19:487-94.
97. Gallant JE, DeJesus E, Arribas JR, Pozniak AL, Gazzard B, Campo RE et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med* 2006; 354:251-260.
98. Gallant J, Pozniak A, DeJesus E, Arribas J, Campo R, Chen SS et al. Efficacy and safety of tenofovir DF, emtricitabine and efavirenz compared to fixed dose zidovudine/lamivudine and EFV through 96 weeks in antiretroviral treatment-naïve patients. XVI International AIDS Conference, Toronto, Canada, 2006. Abstract TUPE0064.
99. Saag MS, Cahn P, Raffi F, Wolff M, Pearce D, Molina JM et al. Efficacy and safety of emtricitabine vs stavudine in combination therapy in antiretroviral-naive patients: a randomized trial. *JAMA* 2004; 292:180-189.
100. Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States, Oct 12, 2006. <http://www.aidsinfo.nih.gov/guidelines/> (Accessed: 10.11.2006).
101. Leon A, Martinez E, Mallolas J, Laguno M, Blanco JL, Pumarola T et al. Early virological failure in treatment-naïve HIV-infected adults receiving didanosine and tenofovir plus efavirenz or nevirapine. *AIDS* 2005; 19:213-215.
102. Negredo E, Bonjoch A, Paredes R, Puig J, Clotet B. Compromised immunologic recovery in treatment-experienced patients with HIV infection receiving both tenofovir disoproxil fumarate and didanosine in the TORO studies. *Clin Infect Dis* 2005; 41:901-905.

103. Martinez E, Milinkovic A, de Lazzari E, Ravasi G, Blanco JL, Larrousse M et al. Pancreatic toxic effects associated with the co-administration of didanosine and tenofovir in HIV-infected adults. *Lancet* 2004; 364:65-67.
104. Podzamczar D, Ferrer E, Gatell JM, Niubo J, Dalmau D, Leon A et al. Early virological failure with a combination of tenofovir, didanosine and efavirenz. *Antivir Ther* 2005; 10:171-177.
105. Perez Elias MJ, Moreno S, Gutierrez C, Lopez D, Abaira V, Moreno A, et al. MA. High virological failure rate in HIV patients after switching to a regimen with two nucleoside reverse transcriptase inhibitors plus tenofovir. *AIDS* 2005; 19:695-698.
106. Eron JJ, Yetzer ES, Ruane PJ, Becker S, Sawyer GA, Fisher RL et al. Efficacy, safety, and adherence with a twice-daily combination lamivudine/zidovudine tablet formulation, plus a protease inhibitor, in HIV infection. *AIDS* 2000; 14:671-681.
107. DeJesus E, Herrera G, Teofilo E, Gerstoft J, Buendia CB, Brand JD et al. Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV-infected adults. *Clin Infect Dis* 2004; 39:1038-1046
108. Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JM, Miller MD et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *JAMA* 2004; 292:191-201.
109. Johnson MA, Gathe JC Jr, Podzamczar D, Molina JM, Naylor CT, Chiu YL, et al.. A Once-Daily Lopinavir/Ritonavir-Based Regimen Provides Noninferior Antiviral Activity Compared With a Twice-Daily Regimen. *J Acquir Immune Defic Syndr*. 2006;43:153-160.
110. Maggiolo F, Ripamonti D, Gregis G, Quinzan G, Callegaro A, Arici C et al. Once-a-day therapy for HIV infection: a controlled, randomized study in antiretroviral-naive HIV-1-infected patients. *Antivir Ther* 2003; 8:339-346.
111. Podzamczar D, Ferrer E, Sánchez P, Gatell J, Crespo M, Lonca M et al. A randomized comparison between abacavir and stavudine, both combined with lamivudine/efavirenz, in antiretroviral-naive patients. Final 96-week results of the ABCD Study. 12th Conference on Retrovirus and Opportunistic Infections, Boston 2005 [Abstract 587]
112. Moyle G, Sabin c, Cartledge J, Johnson M, Wilkins E, Churchill D et al. A 48-week, randomized, open-label comparative study of tenofovir DF vs abacavir as substitutes for a thymidine analog in persons with lipoatrophy and sustained virological suppression on HAART. 12th Conference on Retrovirus and Opportunistic Infections, Boston 2005 Abstract 44LB.
113. Gerstoft J, Kirk O, Obel N, Pedersen C, Mathiesen L, Nielsen H. Low efficacy and high frequency of adverse events in a randomized trial of the triple NRTI regimen abacavir, stavudine and didanosine. *AIDS* 2003; 17:2045-2052.
114. Bartlett JA, Johnson2 J, Herrera G, Sosa N, Rodriguez AE, Shaefer MS. Abacavir/Lamivudine (ABC/3TC) in combination with Efavirenz (NNRTI), Amprenavir/Ritonavir (PI) or Stavudine (NRTI): ESS40001(CLASS) preliminary 48 week results. XIV International AIDS Conference, Barcelona, 2002 [Abstract TuOrB1189]
115. Gallant JE, Rodriguez AE, Weinberg W, Young B, Berger D, Lim ML et al. Early Non-Response to Tenofovir DF (TDF) + Abacavir (ABC) and Lamivudine (3TC) in a Randomized Trial Compared to Efavirenz (EFV) + ABC and 3TC: ESS30009 Unplanned Interim Analysis. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, 2003 [Abstract: H-1722a]
116. Gilead. High rate of virologic failure in patients with HIV infection treated with a once-daily triple NRTI regimen containing didanosine, lamivudine, and tenofovir. Gilead Sciences, Inc., October 14, 2003.
117. Iribarren JA, Ramos JT, Guerra L, Coll O, de Jose MI, Domingo P et al. Prevención de la transmisión vertical y tratamiento de la infección por VIH-1 en la mujer embarazada. Recomendaciones de GESIDA-SEIMC, Asociación Española de Pediatría (AEP), Plan Nacional sobre el Sida y Sociedad Española de Ginecología y Obstetricia (SEGO). *Enferm Infecc Microbiol Clin* 2001; 19:314-35.
118. Van Leth F, Phanuphak P, Ruxrungtham K, Baraldi E, Miller S, Gazzard B et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus

- stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet* 2004; 363:1253-1263.
119. Robbins GK, De Gruttola V, Shafer RW, Smeaton LM, Snyder SW, Pettinelli C et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med* 2003; 349:2293-2303.
 120. Montaner JSG, Schutz M, Schwartz R, Jayaweera D, Burnside AF, Walmsley S et al. Efficacy, safety and pharmacokinetics of once-daily saquinavir soft-gelatin capsule/ritonavir in antiretroviral-naive, HIV-infected patients. *eJIAS* <http://www.medscape.com/viewarticle/528558> (accessed 10.11.06)
 121. Murphy R, da Silva B, McMillan F, Hicks C, Eron J, Wolfe P et al. Seven year follow-up of a lopinavir/ritonavir-based regimen in antiretroviral-naive subjects. 10th European AIDS Conference. November 17-20, 2005. Dublin. Abstract PE7.9/3.
 122. Awni W, Chiu YL, Zhu T, Braun N, Klein C, Heuser R, et al. Significantly reduced food effect and pharmacokinetic variability with a novel lopinavir/ritonavir tablet formulation. 3rd IAS Conference on HIV Pathogenesis and Treatment. Rio de Janeiro, Brazil. July 24-27, 2005. Abstract No. WeOa0206.
 123. Kirk O, Katvenstein TL, Gerstoft J, Mathiesen L, Nielsen H, Pedersen C et al. Combination therapy containing ritonavir plus saquinavir has superior short-term antiretroviral efficacy: a randomized trial. *AIDS* 1999; 13:9-16.
 124. Rodriguez-French A, Boghossian J, Gray GE, Nadler JP, Quinones AR, Sepulveda GE et al. The NEAT Study: A 48-week open-label study to compare the antiviral efficacy and safety of GW433908 versus nelfinavir in antiretroviral therapy naïve HIV-1-infected patients. *J Acquir Immune Defic Syndr* 2004; 35:22-32.
 125. Gathe JC, Jr., Ive P, Wood R, Schurmann D, Bellos NC, DeJesus E et al. SOLO: 48-week efficacy and safety comparison of once-daily fosamprenavir /ritonavir versus twice-daily nelfinavir in naïve HIV-1-infected patients. *AIDS* 2004; 18:1529-1537.
 126. Sanne I, Piliero P, Squires K, Thiry A, Schnittman S. Results of a phase 2 clinical trial at 48 weeks (AI424-007): a dose-ranging, safety, and efficacy comparative trial of atazanavir at three doses in combination with didanosine and stavudine in antiretroviral-naive subjects. *J Acquir Immune Defic Syndr* 2003; 32:18-29.
 127. Murphy RL, Sanne I, Cahn P, Phanuphak P, Percival L, Kelleher T et al. Dose-ranging, randomized, clinical trial of atazanavir with lamivudine and stavudine in antiretroviral-naive subjects: 48-week results. *AIDS* 2003; 17:2603-2614.
 128. Wood R, Phanuphak P, Cahn P, Pokrovskiy V, Rozenbaum W, Pantaleo G et al. Long-Term Efficacy and Safety of Atazanavir With Stavudine and Lamivudine in Patients Previously Treated With Nelfinavir or Atazanavir. *J Acquir Immune Defic Syndr* 2004; 36:684-692.
 129. Malan N, Krantz E, Davil N, Kastango K, Frederick D, Matthew M et al. Efficacy and safety of atazanavir-based therapy in antiretroviral naïve HIV-1 infected subjects, both with and without ritonavir: 48 week results from AI424-089. 13 th Conference on Retrovirus and Opportunistic Infection, Denver, February 5-8, 2006 Abstract 107LB
 130. Eron J, Jr., Yeni P, Gathe J, Jr., Estrada V, DeJesus E, Staszewski S et al. The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. *Lancet* 2006; 368:476-482. 131. Lucas GM, Chaisson RE, Moore RD. Highly active antiretroviral therapy in a large urban clinic: risk factors for virologic failure and adverse drug reactions. *Ann Intern Med* 1999; 131:81-7.
 132. Ledergerber B, Egger M, Opravil M, Telenti A, Hirschel B, Battegay M et al. Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients: a prospective cohort study. *Swiss HIV Cohort Study. Lancet* 1999; 353:863-8.
 133. Klein MB, Willemot P, Murphy T, Lalonde RG. The impact of initial highly active antiretroviral therapy on future treatment sequences in HIV infection. *AIDS* 2004; 18:1895-1904.

134. Gratacos L, Tuset M, Codina C, Miro JM, Mallolas J, Miserachs N et al. Tratamiento antirretroviral de la infección por el virus de la inmunodeficiencia humana: duración y motivos de cambio del primer esquema terapéutico en 518 pacientes. *Med Clin (Barc)* 2006; 126:241-245.
135. Wainberg MA, Turner D. Resistance issues with new nucleoside/nucleotide backbone options. *J Acquir Immune Defic Syndr* 2004; 37 Suppl 1:S36-S43.
136. Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med* 2000; 133:21-30.
137. Chesney MA, Ickovics J, Hecht FM, Sikipa G, Rabkin J. Adherence: a necessity for successful HIV combination therapy. *AIDS* 1999; 13(Suppl A):271-8.
138. Haubrich RH, Little SJ, Currier JS, Forthal DN, Kemper CA, Beall GN et al. The value of patient-reported adherence to antiretroviral therapy in predicting virologic and immunologic response. California Collaborative Treatment Group. *AIDS* 1999; 13:1099-107.
139. Little SJ, Holte S, Routy JP, Daar ES, Markowitz M, Collier AC et al. Antiretroviral-drug resistance among patients recently infected with HIV. *N Engl J Med* 2002; 347:385-94.
140. Bennett D, Smith A, Heneine W, McCormick L, Zaidi I, Garcia-Lerma G et al. Geographic variation in prevalence of mutations associated with resistance to antiretroviral drugs among drug-naive persons newly diagnosed with HIV in ten US cities, 1997-2001. 2nd IAS Conference on HIV Pathogenesis and Treatment, Paris, 2003 [Abstract 787]
141. Phillips NA, Miller V, Sabin C, Cozzi Lepri A, Klauke S, Bickel M et al. Durability of HIV-1 viral suppression over 3.3 years with multi-drug antiretroviral therapy in previously drug-naive individuals. *AIDS* 2001; 15:2379-84.
142. Cohen SJW, Wensing AM, Kovacs C, Righart M, de Jong D, Kaye S et al. Transient relapses ("blips") of plasma HIV RNA levels during HAART are associated with drug resistance. *J Acquir Immune Defic Syndr* 2001; 28:105-13.
143. Sungkanuparph S, Overton ET, Seyfried W, Groger RK, Fraser VJ, Powderly WG. Intermittent episodes of detectable HIV viremia in patients receiving nonnucleoside reverse-transcriptase inhibitor-based or protease inhibitor-based highly active antiretroviral therapy regimens are equivalent in incidence and prognosis. *Clin Infect Dis* 2005; 41:1326-1332.
144. Lichtenstein KA, Armon C, Moorman AC, Wood KC, Holmberg SD. A 7-year longitudinal analysis of IL-2 in patients treated with highly active antiretroviral therapy. *AIDS* 2004; 18:2346-2348.
145. López J, Miró J, Moreno S, Rubio R, Mahillo B, Cifuentes C, et al. Interleukin-2 as treatment for immunological discordant patients with low CD4 cell counts after at least one year of HAART-Gesidad33/03. 10th European AIDS Conference, Dublin, Abstract PS3/1, 2005
146. Berenguer J, Ribera Santasusana J, Rubio R, Miralles P, Mahillo B, Téllez M et al. Characteristics and outcome of AIDS-related non-Hodgkin's lymphoma in patients treated with HAART. 13th Conference on Retrovirus and Opportunistic Infection, Denver, February 5-8, 2006 Abstract 829.
147. Baxter JD, Mayers DL, Wentworth DN, Neaton JD, Hoover ML, Winters MA et al. A randomized study of antiretroviral management based on plasma genotypic antiretroviral resistance testing in patients failing therapy. CPCRA 046 Study Team for the Terry Bein Community Programs for Clinical Research on AIDS. *AIDS* 2000; 14:83-93.
148. Jemsek J, Hutcherson P, Harper E. Poor virologic responses and early emergence of resistance in treatment naive, HIV-infected patients receiving a once daily triple nucleoside regimen of didanosine, lamivudine, and tenofovir DF. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, 2004 [Abstract 51]
149. Landman R, Peytavin G, Descamps D, Brun Vezein F, Benech H, Benalisherif A et al. Low genetic barrier to resistance is a possible cause of early virologic failures in once-daily regimen of abacavir, lamivudine, and tenofovir: The Tonus study. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, 2004 [Abstract 52]

150. KATVenstein DA, Bosch RJ, Hellmann N, Wang N, Bacheler L, Albrecht MA. Phenotypic susceptibility and virological outcome in nucleoside-experienced patients receiving three or four antiretroviral drugs. *AIDS* 2003; 17:821-830.
151. Shafer RW, Stevenson D, Chan B. Human Immunodeficiency Virus Reverse Transcriptase and Protease Sequence Database. *Nucleic Acids Res* 1999; 27:348-52.
152. Le Moing V, Chene G, Carrieri MP, Alioum A, Brun-Vezinet F, Piroth L et al. Predictors of virological rebound in HIV-1-infected patients initiating a protease inhibitor-containing regimen. *AIDS* 2002; 16:21-9.
153. Durant J, Clevenbergh P, Garraffo R, Halfon P, Icard S, del Giudice P et al. Importance of protease inhibitor plasma levels in HIV-infected patients treated with genotypic-guided therapy: pharmacological data from the Viradapt Study. *AIDS* 2000; 14(10):1333-9.
154. Hoetelmans RM, Reijers MH, Weverling GJ, Ten Kate RW, Wit FW, Mulder JW et al. The effect of plasma drug concentrations on HIV-1 clearance rate during quadruple drug therapy. *AIDS* 1998; 12:111-5.
155. Molla A, Korneyeva M, Gao Q, Vasavanonda S, Schipper PJ, Mo HM et al. Ordered accumulation of mutations in HIV protease confers resistance to ritonavir. *Nat Med* 1996; 2:760-6.
156. Kemper CA, Witt MD, Keiser PH, Dube MP, Forthal DN, Leibowitz M et al. Sequencing of protease inhibitor therapy: insights from an analysis of HIV phenotypic resistance in patients failing protease inhibitors. *AIDS* 2001; 15:609-15.
157. Colonna R, Rose R, McLaren C, Thiry A, Parkin N, Friborg J. Identification of I50L as the signature atazanavir (ATV)-resistance mutation in treatment-naive HIV-1-infected patients receiving ATV-containing regimens. *J Infect Dis* 2004; 189:1802-1810.
158. Condra JH, Petropoulos CJ, Ziermann R, Schleif WA, Shivaprakash M, Emini EA. Drug resistance and predicted virologic responses to human immunodeficiency virus type 1 protease inhibitor therapy. *J Infect Dis* 2000; 182:758-65.
159. Bongiovanni M, Bini T, Capetti A, Trovati S, Di BA, Tordato F et al. Long-term antiretroviral efficacy and safety of lopinavir/ritonavir in HAART-experienced subjects: 4 year follow-up study. *AIDS* 2005; 19:1934-1936.
160. De Mendoza C, Martin-Carbonero L, Barreiro P, Diaz B, Valencia E, Jimenez-Nacher I et al. Salvage treatment with lopinavir/ritonavir (Kaletra) in HIV-infected patients failing all current antiretroviral drug families. *HIV Clin Trials* 2002; 3:304-9.
161. Eron JJ, Feinberg J, Kessler HA, Horowitz HW, Witt MD, Carpio FF et al. Once-daily versus twice-daily lopinavir/ritonavir in antiretroviral-naive HIV-positive patients: a 48-week randomized clinical trial. *J Infect Dis* 2004; 189:265-272.
162. Mocroft A, Phillips NA, Miller V, Gatell J, van Lunzen J, Parkin JM et al. The use of and response to second-line protease inhibitor regimens: results from the EuroSIDA study. *AIDS* 2001; 15:201-9.
163. Walmsley SL, Kelly DV, Tseng AL, Humar A, Harrigan PR. Non-nucleoside reverse transcriptase inhibitor failure impairs HIV-RNA responses to efavirenz-containing salvage antiretroviral therapy. *AIDS* 2001; 15:1581-4.
164. Latham V, Stebbing J, Mandalia S, Michailidis C, Davies E, Bower M et al. Adherence to trizivir and tenofovir as a simplified salvage regimen is associated with suppression of viraemia and a decreased cholesterol. *J Antimicrob Chemother* 2005; 56:186-189.
165. Elzi L, Hirsch HH, Battegay M. Once-daily directly observed therapy lopinavir/ritonavir plus indinavir as a protease inhibitor-only salvage therapy in heavily pretreated HIV-1-infected patients: a pilot study. *AIDS* 2006; 20:129-131.
166. Mitty J, Mwamburi D, Macalino G, Caliendo A, Bazerman L, Flanigan T. Improved virologic outcomes and less HIV resistance for HAART-experienced substance users receiving modified directly observed therapy: results from a randomized controlled trial. 13th Conference on Retroviruses and Opportunistic Infections 2006, Denver, Colorado. Abstract 622a.
167. Palella F, Armon C, Cmiel J, Buchacz K, Novak R, Moorman A et al. Enhanced survival associated with use of HIV susceptibility testing among HAART-experienced patients in the HIV Out-

- patient Study (HOPS). 13th Conference on Retroviruses and Opportunistic Infections 2006, Denver, Colorado Abstract 654
168. Barreiro P, Camino N, de MC, Valer L, Nunez M, Martin-Carbonero L et al. Comparison of the efficacy, safety and predictive value of HIV genotyping using distinct ritonavir-boosted protease inhibitors. *Int J Antimicrob Agents* 2002; 20:438-443.
 169. Best B, Witt M, Goicoechea M, Kemper C, Larsen R, Diamond C et al. Improved ART exposure with therapeutic drug monitoring. 13th Conference on Retroviruses and Opportunistic Infections 2006, Denver, Colorado. Abstract 589.
 170. Winston A, Hales G, Amin J, van SE, Cooper DA, Emery S. The normalized inhibitory quotient of boosted protease inhibitors is predictive of viral load response in treatment-experienced HIV-1-infected individuals. *AIDS* 2005; 19:1393-1399.
 171. Larder BA, Hertogs K, Bloor S, van den Eynde CH, DeCian W, Wang Y et al. Tipranavir inhibits broadly protease inhibitor-resistant HIV-1 clinical samples. *AIDS* 2000; 14:1943-1948.
 172. Hicks CB, Cahn P, Cooper DA, Walmsley SL, Katlama C, Clotet B et al. Durable efficacy of tipranavir-ritonavir in combination with an optimised background regimen of antiretroviral drugs for treatment-experienced HIV-1-infected patients at 48 weeks in the Randomized Evaluation of Strategic Intervention in multi-drug resistant patients with Tipranavir (RESIST) studies: an analysis of combined data from two randomised open-label trials. *Lancet* 2006; 368:466-475.
 173. Arasteh K, Clumeck N, Pozniak A, Lazzarin A, De MS, Muller H et al. TMC114/ritonavir substitution for protease inhibitor(s) in a non-suppressive antiretroviral regimen: a 14-day proof-of-principle trial. *AIDS* 2005; 19:943-947.
 174. Lazzarin A, Queiroz-Telles F, Frank I, Rockstroh J, Walmsley S, De Paepe E et al. TMC114 provides durable viral load suppression in treatment-experienced patients: POWER 1 and 2 combined week 48 analysis. XVI International AIDS Conference, Toronto, Canada, 2006 Abstract TUAB0104.
 175. Saag M, Falcon R, Lefebvre E. Efficacy and safety results of darunavir/r in treatment-experienced patients: POWER 3. 44th Annual meeting of the Infectious Disease Society of America. 2006. Toronto, Canada. Abstract 957.
 176. De Meyer S, Vangeneugden T, Lefebvre E, Azijn H, De Baere I, Van Baelen B et al. Phenotypic and genotypic determinants of resistance to TMC114: pooled analysis of POWER 1, 2 and 3. XV International HIV Drug Resistance Workshop. 2006; Sitges, Spain. Abstract 73.
 177. Lalezari JP, Henry K, O'Hearn M, Montaner JS, Piliero PJ, Trottier B et al. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. *N Engl J Med* 2003; 348:2175-85.
 178. Lazzarin A, Clotet B, Cooper D, Reynes J, Arasteh K, Nelson M et al. Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. *N Engl J Med* 2003; 348:2186-95.
 179. Katlama C, Arasteh K, Clotet B. Enfuvirtide TORO studies: 48 week results confirm 24 week findings. 2nd IAS Conference on HIV Pathogenesis and Treatment, Paris, 2003 [Abstract LB2]
 180. Trottieri B, Arasteh K, Henry K, Katlama C, Lazzarin A, Montaner J et al. Durability of Response of Enfuvirtide through 48 Weeks in the TORO Trials. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, 2003 [Abstract: H-835].
 181. Montaner J, Guimaraes D, Chung J, Gafoor Z, Salgo M, DeMasi R. Prognostic staging of extensively pretreated patients with advanced HIV-1 disease. *HIV Clin Trials* 2005; 6:281-290.
 182. Raffi F, Katlama C, Saag M, Wilkinson M, Chung J, Smiley L et al. Week-12 response to therapy as a predictor of week 24, 48, and 96 outcome in patients receiving the HIV fusion inhibitor enfuvirtide in the T-20 versus Optimized Regimen Only (TORO) trials. *Clin Infect Dis* 2006; 42:870-877.
 183. Dailly E, Gagnieu MC, Allavena C, Raffi F, Jolliet P. No significant influence of saquinavir hard-gel capsule administration on pharmacokinetics of lopinavir in combination with ritonavir: a population approach. *Ther Drug Monit* 2005; 27:782-784.

184. Ribera E, Lopez RM, Diaz M, Pou L, Ruiz L, Falco V et al. Steady-state pharmacokinetics of a double-boosting regimen of saquinavir soft gel plus lopinavir plus minidose ritonavir in human immunodeficiency virus-infected adults. *Antimicrob Agents Chemother* 2004; 48:4256-4262.
185. Khanlou H, Graham E, Brill M, Farthing C. Drug interaction between amprenavir and lopinavir/ritonavir in salvage therapy. *AIDS* 2002; 16:797-8.
186. Kashuba AD, Tierney C, Downey GF, Acosta EP, Vergis EN, Klingman K et al. Combining fosamprenavir with lopinavir/ritonavir substantially reduces amprenavir and lopinavir exposure: ACTG protocol A5143 results. *AIDS* 2005; 19:145-152.
187. Ribera E, Azuaje C, Lopez RM, Diaz M, Feijoo M, Pou L et al. Atazanavir and lopinavir/ritonavir: pharmacokinetics, safety and efficacy of a promising double-boosted protease inhibitor regimen. *AIDS* 2006; 20:1131-1139.
188. Deeks SG, Barbour JD, Martin JN, Swanson MS, Grant RM. Sustained CD4+ T cell response after virologic failure of protease inhibitor-based regimens in patients with human immunodeficiency virus infection. *J Infect Dis* 2000; 181:946-953.
189. Grabar S, Le Moing V, Goujard C, Leport C, Kazatchkine MD, Costagliola D et al. Clinical outcome of patients with HIV-1 infection according to immunologic and virologic response after 6 months of highly active antiretroviral therapy. *Ann Intern Med* 2000; 133:401-410.
190. Deeks SG, Barbour JD, Grant RM, Martin JN. Duration and predictors of CD4 T-cell gains in patients who continue combination therapy despite detectable plasma viremia. *AIDS* 2002; 16:201-7.
191. Deeks SG, Martin JN. Reassessing the goal of antiretroviral therapy in the heavily pre-treated HIV-infected patient. *AIDS* 2001; 15:117-9.
192. Youle M. Salvage treatment in HIV disease. *Int J STD AIDS* 2001; 12:286-94.
193. Anderson AM, Bartlett JA. Changing antiretroviral therapy in the setting of virologic relapse: review of the current literature. *Curr HIV/AIDS Rep* 2006; 3:79-85.
194. Ribera E, Aguirrebengoa K, Miralles C, Antela A, Rivero A, Arribas JR. Simplificación del tratamiento antiretroviral. *Enferm Infecc Microbiol Clin* 2002; 20 Suppl 2:48-57.
195. Havlir DV, Marschner IC, Hirsch MS, Collier AC, Tebas P, Bassett RL et al. Maintenance antiretroviral therapies in HIV infected patients with undetectable plasma HIV RNA after triple-drug therapy. AIDS Clinical Trials Group Study 343 Team. *N Engl J Med* 1998; 339:1261-1268
196. Reijers MH, Weverling GJ, Jurriaans S, Wit FW, Weigel HM, Ten Kate RW et al. Maintenance therapy after quadruple induction therapy in HIV-1 infected individuals: Amsterdam Duration of Antiretroviral Medication (ADAM) study. *Lancet* 1998; 352:185-190.
197. Flandre P, Raffi F, Descamps D, Calvez V, Peytavin G, Meiffredy V et al. Final analysis of the Trilege induction-maintenance trial: results at 18 months. *AIDS* 2002; 16:561-568.
198. Cooper DA, Emery S. Therapeutic strategies for HIV infection--time to think hard. *N Engl J Med* 1998; 339:1319-1321.
199. Arribas JR, Pulido F, Delgado R, Lorenzo A, Miralles P, Arranz A et al. Lopinavir/ritonavir as single-drug therapy for maintenance of HIV-1 viral suppression: 48-week results of a randomized, controlled, open-label, proof-of-concept pilot clinical trial (OK Study). *J Acquir Immune Defic Syndr* 2005; 40:280-287.
200. Arribas JR, Pulido F, Delgado R, Cabrero E, Cepeda C, Gonzalez-Garcia J et al. Lopinavir/ritonavir as single-drug maintenance therapy in patients with HIV-1 viral suppression: Forty eight week results of a randomized, controlled, open label, clinical trial (OK04 Study). XVI International AIDS Conference, Toronto, Canada, 2006 Abstract THLB0203
201. Swindells S, DiRienzo AG, Wilkin T, Fletcher CV, Margolis DM, Thal GD, et al. Regimen simplification to atazanavir-ritonavir alone as maintenance antiretroviral therapy after sustained virologic suppression. *JAMA*. 2006;296:806-814.
202. Martinez E, Arnaiz JA, Podzamczar D, Dalmau D, Ribera E, Domingo P et al. Substitution of nevirapine, efavirenz, or abacavir for protease inhibitors in patients with human immunodeficiency virus infection. *N Engl J Med* 2003; 349:1036-1046.

203. Gatell JM, Salmon-Ceron D, Lalezari A, Van Wijngaerden E, Antunes F, Leen C et al. Efficacy and safety of atazanavir based HAART in patients switching from a stable boosted/unboosted protease inhibitor treatment: the SWAN Study. 10th European AIDS Conference. November 17-20, 2005. Dublin. Abstract PS1/1