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# Protease Inhibitors as Preferred Initial Regimen for Antiretroviral-Naive HIV Patients

*Francisco Tejerina and Juan Carlos López Bernaldo de Quirós*
*Infectious Diseases Unit/HIV, Gregorio Marañón University Hospital, Madrid, Spain*

## Abstract

***At present, the majority of patients who have initiated their first antiretroviral therapy have received a combination comprising a nonnucleoside and two nucleoside analogues. The use of nonnucleosides as first-line therapy has been favored for their more convenient dosing, with less pill numbers, and the possibility of co-formulation with nucleoside analogues. Although protease inhibitors are also considered to be a preferred standard, they have been less frequently used as first regimen of choice because of their adverse effects in the short to medium term. The introduction of darunavir and atazanavir as new protease inhibitors boosted with ritonavir has resulted in a significant change in this area. These drugs show a lower incidence of adverse effects, allow once-a-day administration, and have a high barrier to resistance that prevents the selection of resistance mutations in case of virologic failure. On this basis, it is likely that over the next few years these drugs will become a standard of care, gaining acceptance and being used more frequently as preferred first-line regimen.*** **(AIDS Rev. 2011;13:227-33)**

*Corresponding author: Juan Carlos López Bernaldo de Quirós, juanclopezbq@wanadoo.es*

## Key words

***Protease inhibitors. Darunavir. Atazanavir. Naive patients.***

## Introduction

Current guidelines for antiretroviral therapy for treatment-naive patients recommend the use of two nucleoside reverse transcriptase inhibitors (NRTI) plus a third agent to be chosen between a nonnucleoside reverse transcriptase inhibitor (NNRTI), a ritonavir-boosted protease inhibitor (PI/r), or an integrase inhibitor (INI). For the two NRTI, fixed-dose combinations of abacavir/lamivudine (ABC/3TC) or tenofovir/emtricitabine (TDF/FTC)[1-5] are recommended. However, at present, a co-formulation of efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC) is probably the most frequently used combination due to its simplicity, effectiveness, and well-known adverse effects. Nonetheless, the development of new PI/r that have lower rates of adverse effects and are well tolerated may cause these preferences to be reversed in coming years, so we may see an increase in the guidelines and recommendations including this class of drugs.

In this article we review the advantages and drawbacks of starting treatment with the antiretroviral combinations recommended in treatment guidelines, with special attention paid to those that include PI/r. Therefore, we will focus only on those combinations recommended by the majority of antiretroviral therapy guidelines (Table 1).

**Correspondence to:**
Juan Carlos López Bernaldo de Quirós
Unidad de Enfermedades Infecciosas/VIH
Hospital Universitario Gregorio Marañón
Dr. Esquerdo, 46
28007 Madrid, España
E-mail: juanclopezbq@wanadoo.es

## Nonnucleoside reverse transcriptase inhibitor-based regimens

One of the antiretroviral drugs for which most clinical experience is available is efavirenz (EFV). The DMP-006 study compared it to indinavir, the preferred PI at that time, and showed that it had greater virologic efficacy at 48 as well as at 144 weeks of follow-up[6]. Since then, the efficacy and safety of EFV has been extensively documented and it was compared to nevirapine in the 2NN study[7], to lopinavir/r (LPV/r) in the ACTG-5142

**Table 1. Preferred combinations recommended by the guidelines for the use of antiretroviral therapy**

| IAS[1] | EACS[2] | DHHS[3] | Gesida/PNS[4] | BHIVA[5] |
|---|---|---|---|---|
| EFV/TDF/FTC<br>TDF/FTC + DRV/r<br>TDF/FTC + ATV/r<br>TDF/FTC + RAL | TDF/FTC<br>or<br>ABC/3TC<br>+<br>EFV or<br>NVP or<br>DRV/r or<br>ATV/r or<br>LPV/r or<br>SQV/r or<br>RAL | EFV/TDF/FTC<br>DRV/r + TDF/FTC<br>ATV/r + TDF/FTC<br>RAL + TDF/FTC<br>LPV/r + ZDV/3TC* | TDF/FTC/EFV<br>TDF/FTC + DRV/r<br>TDF/FTC + ATV/r<br>TDF/FTC + RAL†<br>TDF/FTC + NVP†<br>TDF/FTC + LPV/r†<br>ABC/3TC + ATV/r†<br>ABC/3TC + LPV/r†<br>ABC/3TC + EFV† | EFV/TDF/FTC<br>EFV + ABC/3TC |

TDF: tenofovir; FTC: emtricitabine; EFV: efavirenz; DRV/r: darunavir/ritonavir; ATV/r: atazanavir/ritonavir; SQV/r: saquinavir/ritonavir; RAL: raltegravir; NVP: nevirapine; LPV/r: lopinavir/ritonavir; ABC: abacavir; 3TC: lamivudine; ZDV: zidovudine.
*Combination of choice for pregnant women.
†These guidelines are not recommended by the entire GESIDA panel of experts as preferred treatment options.

trial[8], and with atazanavir/r (ATV/r) in the ACTG 5202 trial[9]. In comparison with LPV/r or nevirapine, EFV showed lower rates of treatment failure along with a lower incidence of adverse effects leading to discontinuation of treatment. However, in comparison with atazanavir/r, no significant differences were found between the two drugs when combined with either ABC/3TC or with TDF/FTC.

Efavirenz has a long half-life (approximately 52 hours), which makes once-daily dosing possible, and is currently co-formulated into a single tablet[10]. Making it possible to administer a single tablet once daily is what has led to the widespread use of this combination at present. In comparison to what are considered the classic PI/r, it has a better lipid profile although its triglyceride levels are higher than that of other drugs in the same class. However, these advantages are to a large extent reduced when it is compared to ATV/r and darunavir/r (DRV/r).

On the negative side, EFV has a low barrier to resistance so that a single mutation can cause a large reduction in sensitivity to the drug. Because of this, in cases where patient adherence with therapy is in doubt, it is preferable to not use this drug to avoid limiting future treatment options. Another negative aspect is that EFV commonly causes neuropsychiatric adverse effects, such as depression, sleep disturbances, and dizziness, that may sometimes lead to treatment discontinuation.

## Integrase inhibitor-based regimens

At present, raltegravir (RAL) is the only integrase inhibitor on the market. It is a drug with potent antiviral activity that undergoes hepatic metabolism with no effect on cytochrome 3A4 and for which no dosage adjustment is required in patients with moderate renal or hepatic impairment. It was compared to EFV administered twice-daily in combination with TDF/FTC to treatment-naive patients in the STARTMRK trial[11]. Raltegravir showed non-inferiority compared to EFV and even exhibited a more favorable lipid profile. In contrast to EFV, RAL achieves an undetectable plasma viral load more quickly, although for the time being this has not been found to have a clinically meaningful effect. Perhaps the most striking feature of this drug is its good safety profile and minimal rate of clinical or laboratory adverse effects. Likewise, the absence of interactions with other drugs makes it a useful drug for patients on multiple medications.

The main drawback of RAL is the need for it to be administered twice a day. The QDMRK trial evaluated the possibility of once-daily dosing with RAL. However, the drug levels achieved were lower and associated with a higher rate of virologic failure[12]. A second drawback of this drug is that it has a low barrier to resistance so that it only requires the development of a single mutation for resistance to appear and this at times can condition cross-resistance to other INI[13]. A third additional problem is its higher cost compared with other initial therapy options.

## Protease inhibitor-based regimens

The introduction of the first PI for the treatment of HIV dramatically improved the prognosis for patients with HIV infection. However, the first generation of these drugs (indinavir, saquinavir, nelfinavir) were associated

with significant adverse effects and required treatment with a large number of pills, administration two or three times a day and even strict dietary restrictions. Boosting PI with ritonavir improved therapeutic efficacy, though at times this improvement has been canceled out by the emergence of adverse effects that have led to treatment failure. These adverse effects are the reason why over the last several years NNRTI have come into widespread use in initial therapy. As we have mentioned before, present guidelines recommend the use of ATV/r (300/100 mg QD) or DRV/r (800/100 mg once daily) as PI/r, and reserve use of LPV/r as an alternative regimen or as first-choice therapy for pregnant women. Both ATV/r and DRV/r have demonstrated high virologic efficacy with a low rate of adverse effects leading to discontinuation of treatment. Yet another advantage, which is common to all PI/r, is the low selection of resistance mutations when virologic failure occurs. That, together with their long half-life allows a measure of "forgiveness" so that if the patient forgets to take a pill once, the risk of having a mutation will be minimal. Although PI/r were traditionally associated with worse metabolic and lipid profiles, both ATV/r and DRV/r have improved substantially in this regard and may be considered to be PI with a more favorable lipid profile.

The major drawbacks of these drugs are the need for a greater number of pills, a cost that is somewhat higher than that of NNRTI, and the need for boosting with ritonavir. From a pharmacokinetic point of view, these new antiretroviral drugs have slightly more number of drug interactions, and dosage adjustments for other medications need to be made. Finally, there are some concerns about their penetration in the CNS, especially when taken together with TDF/FTC. However, it has been described with other antiretroviral drugs, including efavirenz, and so far the clinical relevance of the penetration of antiretroviral drugs in the CNS is unclear[14].

## *Atazanavir/ritonavir*

Atazanavir/r has been compared to drugs, which, at the time of its approval, were considered the regimens of choice for treatment-naive patients. Thus, in the Castle study it was compared to LPV/r[15] and in the ACTG-5202 study it was compared to EFV[9]. More than 800 treatment-naive patients were enrolled in the Castle study. After 96 weeks of follow-up, 74% of patients receiving ATV/r had a plasma viral load of < 50 copies/ml compared to 68% in the LPV/r arm (estimated difference: 6.1; 95% CI: 0.3-12.0%). It was determined that these differences mainly resulted from more frequent discontinuation of treatment in the LPV/r arm due to adverse side effects.

In the ACTG-5202 study, ATV/r was compared to EFV in a four-way comparison that also included the use of two fixed-dose co-formulations of two NRTI. After 96 weeks there were no significant differences in non-progression to virologic or treatment failure between the two drugs, regardless of the NRTI combination used; 83.4% for ATV/r vs. 85.3% for EFV in association with ABC/3TC and 89 vs. 89.8%, respectively, in combination with TDF/FTC. Regarding safety, patients who received EFV in combination with ABC/3TC experienced adverse effects sooner than those who were in the ATV/r arm.

The main adverse effects associated with ATV/r are: indirect hyperbilirubinemia, which, although not accompanied by elevation of transaminases, does cause discoloration of the sclera[16], and the association between exposure to ATV/r and nephrolithiasis, which has been reported on several occasions[17,18]. In addition to these, it is recommended that co-administration with proton pump inhibitors be avoided[16].

A sub-study of ACTG-5202 that analyzes, among other things, the efficacy of EFV or ATV/r according to patient gender and race has been published recently[19]. The results showed that women who received ATV/r treatment had a higher risk of virologic failure than men. This is the first study to show this effect, so further studies will be necessary to understand the true clinical relevance of these results.

## *Darunavir/ritonavir*

The Artemis trial compared DRV/r to LPV/r, which at the time was the preferred PI/r, in treatment-naive patients[20]. The doses used were 800 mg of darunavir and 100 mg of ritonavir. A total of 689 patients were included in the study. After 96 weeks, 79% of patients receiving DRV/r had a PVL of < 50 copies/ml compared to 71% in the LPV/r arm (estimated difference: 8.4%; 95% CI: 1.9-14.8%). In this case, the differences between the two arms of the study were due to a more favorable safety profile of DRV/r, which had a lower rate of adverse effects leading to discontinuation of treatment than LPV/r (4 vs. 9%), as well as there being a smaller number of virologic failures in the DRV/r arm than in the LPV/r arm (12 vs. 17%; $p = 0.0437$)[20,27]. Likewise, there was a lower incidence of diarrhea in the DRV/r arm than in the LPV/r arm (4 vs. 11%; $p < 0.001$). Darunavir/r also showed a more favorable profile regarding lipid

**Table 2. Comparison of new ritonavir-boosted protease inhibitors (atazanavir/r and darunavir/r) to lopinavir/r with regard to adverse effects and impact on lipid levels**

| | Castle 96 weeks[15] | | Artemis 96 weeks[20] | |
|---|---|---|---|---|
| | LPV/r | ATV/r | LPV/r | DRV/r |
| Adverse effects | | | | |
| Grade 2-4 | 30% | 32% | 34% | 23% |
| Leading to discontinuation | 5% | 2.96% | 10.1% | 5.5% |
| Diarrhea | 17% | 7% | 11% | 4% |
| Increase in lipid levels from baseline | | | | |
| Total Cholesterol* | 36 | 20 | 35 | 26 |
| LDL-Cholesterol* | 17 | 12 | 15 | 17 |
| HDL-Cholesterol* | 10 | 7 | 8 | 5 |
| Triglycerides* | 55 | 14 | 56 | 18 |

LPV/r: lopinavir/ritonavir; ATV/R: atazanavir/ritonavir; DRV/R: darunavir/ritonavir.
*Increase at week 96 from baseline (mg/dl).

parameters with smaller elevations in triglyceride levels (grades 2-4: 4 vs. 13%; $p < 0.001$) and total cholesterol (grades 2-4: 18 vs. 28%; $p < 0.001$).

## Criteria for choosing between protease inhibitor/ritonavir-based and nonnucleoside reverse transcriptase inhibitor-based regimens

There is no single criterion to guide us in choosing between one antiretroviral treatment or another and the factors should be considered as a whole before a decision is made.

### *Efficacy*

Although, in the early years of development of antiretroviral therapy, much emphasis was put on efficacy, over time it has lost some of its importance. This is so because at present all possible third drugs recommended by the guidelines fulfill this criterion. For example, after 48-96 weeks of treatment, EFV just as much as RAL, ATV/r, or DRV/r achieves reduction of viral load in excess of 75% of cases in clinical trials[9,11,15,20]. In addition, in the majority of cases, treatment failure is attributable to adverse effects rather than to lack of antiviral potency.

### *Safety*

The second issue to be considered is adverse effects and safety in the short, medium, and long term. Both EFV and RAL showed good safety profiles in the STARTMRK trial, with rates of discontinuation of treatment due to severe adverse effects related to the drugs of less than 2% (1.4% for RAL vs. 1.8% for EFV; $p > 0.05$)[11]. However, EFV continues to have certain medium- and long-term neuropsychiatric effects that, although they do not affect patient safety, are sufficient cause for discontinuing treatment with EFV even three years after initiating treatment[21]. Likewise, when EFV was compared to ATV/r in the ACTG-5202 study, EFV in combination with ABC/3TC showed a higher rate of adverse effects[9].

As mentioned previously, the new PI/r have better safety profiles than the older ones, with lower rates of adverse effects in general and of those that may lead to discontinuation of antiretroviral therapy (ART) in particular. For example, in the M98-863 study, which led to approval of LPV/r[22], the incidence of diarrhea for LPV/r was 15.6%, whereas it was 7% for ATV/r[15] and 4% for DRV/r[20] (Table 2) in the Castle and Artemis studies, respectively.

One of the big issues that have been associated with PI/r is their worse lipid profiles. However, here too the new PI/r have shown great improvements that reduce the differences with EFV and RAL. For example, in the ACTG-5202 study, ATV/r had a better lipid profile than EFV, with lower increase of total cholesterol and LDL cholesterol both in combination with ABC/3TC as well as with TDF/FTC. On the other hand, triglyceride levels were slightly worse with ATV/r, especially in combination with ABC/3TC[7], and in the ARTEN study, nevirapine provided a better lipid profile than ATV/r[23]. Darunavir/r also has a good lipid profile, with clear differences with respect to LPV/r. In the Artemis study, use of LPV/r was significantly associated with higher elevations in triglyceride levels and total cholesterol[20].

**Table 3. Selection of drug resistance mutations in patients who develop virologic failure using distinct antiretroviral agents**

| | Raltegravir[11]* | Efavirenz[9†] | ATV/r[9†] | DRV/r[27†] |
|---|---|---|---|---|
| Number of patients | 281 | 922 | 926 | 343 |
| Virologic failure | 9.6% | 13.8% | 15% | 12% |
| Genotyped patients | 9 | 111 | 130 | 31 |
| Third drug RM | 4 | 68 | 1‡ | 4‡ |
| NNRTI RM | 3 | 36 | 16 | 2 |

Data on efavirenz and atazanavir/r from ACTG 5202 study groups data on abacavir/lamivudine together with tenofovir/emtricitabine.
ATV/r: atazanavir/ritonavir; DRV/R: darunavir/ritonavir; RM: resistance mutations; NNRTI: nonnucleoside reverse transcriptase inhibitor.
*Results at 48 weeks.
†Results at 96 weeks (5202 and Artemis Antiviral therapy).
‡All resistance mutations in the protease gene were considered to be minor or polymorphisms.

There are currently several ongoing studies that show the benefits for patients, from a lipid perspective, of switching to ATV/r or DRV/r from LPV/r or FPV/r based regimens[24-26].

## *Protease inhibitor resistance*

At the stage where HIV infection can be considered to be a chronic disease and the patient will have to receive treatment for the rest of his life, it is advisable to keep all future treatment options open. The presence of mutations that confer resistance to antiretroviral drugs can reduce these future options, so it should be a priority to prevent their occurrence. This is the main benefit of PI/r over both EFV and RAL (Table 3). These latter two drugs have a low barrier to resistance, so that a single mutation may affect not only resistance to that drug but also to others belonging to the same class, as well to the nucleoside analogs used in combination with them[8,11,13]. By contrast, in patients who experience virologic failure to ATV/r and DRV/r, the frequency of resistance mutations is low, both in the protease gene and in the reverse transcriptase[9,27]. In the case of DRV/r, this even allows patients to be rescued with the same combination that failed and keeps all future treatment options intact.

One feature of resistance mutations that results in favoring the use of PI/r is the transmission of viruses with resistance mutations during primary infection. A recent study estimated the rate of transmission of viruses with resistance mutations at 14.3%, the most frequent being those that affect nonnucleosides, which occurred in 8.3% of cases, and of these, mutation K103N was found in 5.17% of all analyzed sequences[28]. This means that resistance testing should be performed in all patients about to initiate their first ART, especially if starting with EFV. The majority of laboratories that test for antiretroviral drug resistance use genotypic techniques that cannot detect so-called minority variants. To detect these variants, thus named for their presence at extremely low levels in viral quasispecies, more complex and time-consuming techniques that are not available to all clinical laboratories must be used. One meta-analysis estimated the presence of minority variants at 14% and, when NNRTI are used, the increased risk of virologic failure was associated with hazard ratio of 2.3 (95% CI: 1.9-3.5) compared to non-presence of minority variants[29].

Given the higher barrier to resistance of PI/r, the presence of resistance mutations, either in their majority or minority variants, should not constitute a clinical problem for these drugs and their use is to be recommended when the presence of resistance mutations cannot be ruled out before initiation of treatment.

## *Adherence*

From a patient's point of view, adherence to treatment is a fundamental feature and adherence has much to do with convenience. The majority of experts recommend using regimens with a low number of pills that can be administered once a day. Of all the alternatives possible at present, EFV is the only treatment that can be coadministered with TDF/FTC as one pill a day. Therefore, we might consider it to be the most convenient of all. Raltegravir requires only two tablets a day but, as mentioned previously, needs to be taken every 12 hours.

Regimens using the new PI/r can be administered once-daily with a relatively small number of tablets and

have no dietary restrictions nor are they associated with the gastrointestinal side effects of the older PI/r. These issues make ATV/r and DRV/r good options from an adherence perspective. Any potential reduction in adherence would be offset by non-selection of resistance mutations as these are drugs that have a high barrier to resistance. This matter has been well documented in patients receiving DRV/r therapy who, despite suboptimal adherence, were able to maintain a good virologic response without selection of resistance mutations[30].

On the other hand, there are simplification strategies that may help in the choice of initial treatment. The MONET trial recently demonstrated the efficacy of once-daily DRV/r monotherapy as an alternative strategy to maintain virologic suppression in a carefully selected group of patients with different prior antiretroviral treatment histories. This strategy, which differentiates from ATV/r, would avoid the toxicity associated with NRTI, may make treatment more convenient, and thus may improve patient adherence to treatment and help reduce the cost of antiretroviral treatment[31]. However, PI/r monotherapy should be considered as an alternative strategy, and a higher rate of failure compared to standard triple therapy has been reported in some studies[32].

## Under what circumstances should initiation of ritonavir-boosted protease inhibitor-based therapy be advised?

Despite improvements in early diagnosis of HIV infection, a non-negligible number of patients will be diagnosed with HIV after the development of an opportunistic disease or within the context of advanced immunosuppression. Several studies have shown that early initiation of treatment under these circumstances is associated with better outcomes, including lower medium- and long-term mortality[33]. Within this context, and given the need for genotypic resistance testing prior to initiation of treatment with EFV, PI/r enable the immediate initiation of antiretroviral treatment without incurring the risk of virologic failure due to selection of resistance mutations already present in the patient.

Although predicting a treatment-naive patient's adherence to treatment is difficult, in cases where it is suspected that it will be poor it may be advisable to initiate treatment with a PI/r. This would prevent the accumulation of resistance mutations if the patient's level of adherence is not enough. In this regard, it is advisable to initiate treatment with a PI/r for patients who suffer from drug addiction or psychiatric disorders, or those whose job circumstances may result in worse adherence, and those with high viral loads and/or low CD4 counts, all of which have been associated with a higher rate of virologic failure.

Fortunately, the likelihood of parenteral transmission of HIV in patients addicted to drugs has declined in Western countries in recent years. Even so, a significant proportion of patients who were infected through this route are currently enrolled in methadone treatment programs and it is well known that EFV interferes with methadone metabolism. This interaction causes an increase in the methadone dose required, with the attendant risk to the patient, both because the introduction of EFV reduces methadone levels and because if the patient unilaterally decides to stop taking antiretroviral therapy it can lead to overdosing. In such cases, since interactions between PI/r and methadone are lower, circumstances make it advisable to initiate treatment with these drugs[34].

Lastly, the spread of HIV through vertical transmission has virtually disappeared as a means of transmission in Western countries. To achieve this, viral replication must be controlled by the end of pregnancy. The PI/r regimens used during pregnancy, mainly including LPV/r, have shown high efficacy and a good safety profile for both the mother and the newborn infant.

This, together with the fact that EFV has been classified as an FDA Pregnancy Category C drug, has led to treatment guidelines that recommend the use of PI in pregnant women instead of EFV[3].

## Conclusions

The PI/r developed in recent years, ATV/r and DRV/r, have better safety and efficacy profiles than the earlier ones. Their use does not require strict dietary restrictions, there is not a large number of pills to be taken, they can be taken once-daily, and have few or no gastrointestinal side effects. This, together with their high barrier to resistance, to the development of resistance mutations, makes them a valid alternative for patients initiating their first antiretroviral therapy. Their use should be first choice over EFV in those patients whose mutations profile prior to initiation of therapy is unknown, patients of whom poor adherence is suspected, those in certain work settings, patients receiving methadone, and pregnant women. The improved risk/benefit profile of the new PI/r is helping this class of drugs to gain more and more acceptance as an initial treatment option.

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