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Boosted Protease Inhibitor Monotherapy. What Have We Learnt after Seven Years of Research?

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Abstract

Boosted protease inhibitor monotherapy has emerged as an antiretroviral alternative option to avoid the use of nucleosides. After more than seven years of research with hundreds of patients exposed to this kind of therapy, controversy about its use remains. While European and Spanish guidelines for the use of antiretroviral therapy in adults include monotherapy as an alternative for simplification, experts in the USA express the view that this strategy cannot be currently recommended.

Our conclusion, after more than seven years of research, is that simplification of a suppressive triple antiretroviral therapy to boosted protease inhibitor monotherapy has demonstrated safety and efficacy in a high proportion of patients. Although this is not a strategy to implement indiscriminately in all patients, it could be a good option for those patients with toxicity related to nucleoside reverse transcriptase inhibitors, or for trying to avoid such toxicities in virologically controlled patients without previous failure to protease inhibitors, restarting nucleosides if the viral load does not remain undetectable.

If simplification to monotherapy is selected to treat some patients, twice-daily lopinavir/ritonavir, or preferably once-daily darunavir/ritonavir, should be chosen as data with other boosted protease inhibitors are inconclusive or even nonexistent.

Nevertheless, more studies focusing on the control of HIV replication in viral reservoirs with monotherapy, as with triple therapy, are warranted. **(AIDS Rev. 2010;12:127-34)**

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Introduction

Since 1996[1,2] the combination of three antiretroviral drugs has been established as the standard therapy to treat HIV-1 infection. These triple combinations, including two nucleoside reverse transcriptase inhibitors (NRTI) and one nonnucleoside reverse transcriptase inhibitor (NNRTI) or one protease inhibitor (PI), have shown potent and durable suppression of HIV-1 replication, with subsequent improvement of immunological function and an impressive decrease of mortality and morbidity related to AIDS.

Two main groups of rationales have helped these triple combinations to become the paradigm of antiretroviral therapy: historical and scientific reasons. The first are due to the chronological development of antiretroviral drugs. Between 1987 and 1996 only NRTI were available and we learnt that these drugs had a relatively small and transient antiretroviral activity if used as monotherapy. Some improvement in potency and durability was obtained when two of these compounds were combined. This two-NRTI combination

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has been considered as an essential component ("the backbone") of antiretroviral therapy, and subsequent development of new drugs from new families (PI and NNRTI) has been marked for the competition to demonstrate that the new drug was the preferred third drug in the combination.

The scientific reasons are a result of the low potency and low genetic barrier of the NRTI. As a consequence, triple combinations are necessary to achieve enough antiviral potency to suppress viral replication below the detection limits. Triple therapy was also required to avoid the selection of naturally preexistent viruses with drug resistance associated mutations, providing a genetic barrier that ensures protection against viruses with one to three primary mutations. This is relevant because the probability of a single virus with more than three mutations in its genome is very low in previously untreated patients.

However, the extended use of triple therapy has not been exempt from additional problems related to the toxicity of its components, complexity of the regimens, or the elevated cost of the therapy. Different strategies of reducing the number of drugs have been attempted from the very beginning of the "HAART era", trying to solve some of these problems.

Three clinical trials (ACTG 343[3], Trilege[4], ADAMS[5]) first explored the concept of a reduction in the number of drugs in antiretroviral therapy. Unfortunately, these three trials had to be prematurely stopped due to an unacceptable risk of virologic failure in patients maintained with single- or dual-drug regimens. We now know that the antiretroviral drugs used for maintenance therapy in these trials were suboptimal due to their limited potency (nelfinavir), low genetic (lamivudine) or pharmacological barriers (nelfinavir, indinavir) to resistance, and complex dosing schedules (indinavir, nelfinavir/saquinavir).

The development of ritonavir-boosted PI withdrew some of those limitations, increasing potency, genetic barriers, and simplifying posology. These characteristics made boosted PI the perfect candidates to test again the concept of reducing the number of drugs in antiretroviral therapy.

Several reports from small, proof-of-concept studies using indinavir/ritonavir[6] or, mainly, lopinavir/ritonavir (LPV/r)[7-11] as antiretroviral monotherapy have arisen since 2002, starting an investigational line and a therapeutic option that remains active to this day.

In the following review, we will try to summarize what we have learnt of boosted PI monotherapy after more than seven years of research, and to give a personal view of its applicability, based on our experience with this therapy.

Efficacy and clinical scenarios of potential use of monotherapy

The first point that has become clear is that boosted PI monotherapy is not a good option for treating naive patients. First evidences of monotherapy use in this setting came from the IMANI studies. Both IMANI-I[7] and IMANI-II[12] were non-comparative studies starting LPV/r monotherapy in patients naive to antiretrovirals (n = 30 and 39, respectively). In IMANI-I, 60 and 90% had a viral load < 50 copies/ml at 48 weeks with the intent-to treat (ITT) and as-treated analyses, respectively. In IMANI-II, 79 and 74% had a viral load < 75 copies/ml at 48 and 96 weeks, respectively, with the ITT analysis.

The main evidence in this scenario came from the MONARK trial[13]. In this study, 136 naive patients were randomly assigned to receive LPV/r either as monotherapy or with two NRTI (zidovudine and lamivudine). At week 48, the rates of full HIV RNA suppression to < 50 copies/ml were statistically lower for the LPV/r monotherapy arm (67%) than for the LPV/r plus two NRTI arm (75%) in the ITT switch-equals-failure analysis. Five patients on monotherapy developed at least one major PI mutation during the 96 weeks of follow-up (6%). This is higher than expected for boosted PI-based triple therapy in naive patients, but pretty similar to the rate of resistance after starting an efavirenz plus two NRTI regimen (6.16% with resistance to efavirenz and/or NRTI out of 487 patients in the 96 weeks analysis of the 934 Trial)[14]. However, as the authors of the MONARK study affirm, the mutations emerging in those naive patients treated with LPV/r monotherapy did not jeopardize the future therapeutic options in any of them[15].

A second scenario studied has been the use of boosted PI monotherapy in an induction-maintenance strategy. The Abbott M03-613 trial[16] randomized 155 naive patients to receive zidovudine plus lamivudine with efavirenz or LPV/r. The NRTI were stopped in those patients assigned to LPV/r after three HIV RNA tests showing < 50 copies/ml (12 weeks with undetectable HIV RNA). At 96 weeks, statistically less patients taking LPV/r had HIV RNA < 50 copies/ml when the "previous-failure = failure" endpoint was used (48% of those who had received LPV/r versus 61% of those who had received the efavirenz-based combination). However, this is a very unusual endpoint as it

considers every single determination > 50 copies/ml as a treatment failure, even if the following viral loads remained < 50 copies/ml without any change in the randomized therapy. When a standard "ITT non-completion = failure" analysis was used, the two treatment groups had similar proportions of subjects with suppressed HIV-1 RNA loads at week 96. The selected comparator (efavirenz) does not definitively allow knowing if the differences could be explained by the triple versus monotherapy comparison or by the efavirenz versus LPV/r comparison, as one large study (ACTG 5142)[17] has demonstrated better virologic results with efavirenz than with LPV/r-based therapy in naive patients. An interesting finding from the M03-613 trial is a lower development of lipoatrophy in those patients exposed to monotherapy. But the problem, again, is that it is not possible to distinguish clearly if all the effect is a consequence of stopping the NRTI or if it is also due to the potential worse effect of efavirenz on lipoatrophy as seen in the ACTG 5142 study[18].

However, boosted PI monotherapy has shown its best results in simplification studies. This is the scenario with the greater number of studies and experiences. Most of the studies have used LPV/r as monotherapy, but there are also two large randomized trials with darunavir/ritonavir (DRV/r) and four small non-comparative studies with atazanavir/ritonavir (ATV/r). Inclusion criteria and endpoints were heterogeneous, but they have provided enough information on the strengths and limitations of the strategy to make recommendations about when this could, or could not, be implemented.

The biggest published study of simplifying to LPV/r monotherapy is the OK04 trial[19]. In this study, 205 patients taking LPV/r plus two NRTI, with HIV RNA < 50 copies/ml for more than six months and no history of virologic failure while taking a PI, were randomized to continue their triple therapy or to stop the NRTI, remaining with LPV/r in monotherapy for 96 weeks. At 96 weeks, 77.6 and 77.0% remained taking the randomized therapy with a suppressed viral load (< 50 copies/ml)[20]. The main objective of the study was to show the non-inferiority of the strategy of simplification to monotherapy, with reintroduction of NRTI if HIV RNA did not remain < 50 copies/ml. At week 96, the proportion of patients without therapeutic failure according to the primary endpoint definition (for which the 10 patients who reintroduced NRTI at any moment due to confirmed viral load > 50 copies/ml but remained taking LPV/r with HIV RNA < 50 copies/ml at week 96 are not considered as therapeutic failures) was 78% in the triple-therapy group and 87% in the monotherapy group (difference: –9%; 95% CI: –20 to +1.2%; p = 0.09). The upper limit of the confidence interval for the difference (+1.2%) fulfilled the pre-established criteria for non-inferiority of the tested strategy. By observed treatment analysis, in which missing data or change in therapy is censored and re-induction with nucleosides is considered failure, at week 96 94.4% of patients receiving triple therapy had an HIV RNA < 50 copies/ml compared to 86.4% of patients receiving monotherapy (p = 0.06; log rank).

Two patients in the monotherapy arm, but also two other patients in the triple-therapy arm, presented at least one major mutation associated to resistance to lopinavir. Both patients had their HIV re-suppressed to < 50 copies/ml after changing LPV/r to saquinavir/ritonavir. In a combined analysis of the patients taking LPV/r monotherapy in the OK trials[21] (451 patient-years of follow-up), the estimated incidence of resistance to lopinavir was 0.51 per 100 patient-years (95% CI: 0.06-1.82 per 100 patient-years of follow-up).

Another two randomized but smaller trials[22,23], comparing simplification to LPV/r monotherapy versus maintenance with triple therapy, have shown concordant results. Another small comparative study was interrupted because of a predefined stopping rule when six (20%) of the first 30 patients on monotherapy failed to maintain viral suppression[24].

Only one study has tried to simplify to LPV/r monotherapy dosed once-daily[25]. In that study (IMANI III), 31 patients with a viral load < 50 copies/ml while taking LPV/r monotherapy twice-daily were changed to LPV/r monotherapy once-daily. At 48 weeks, 84% remained virologically suppressed, but PI resistance was selected in two of 10 subjects who exhibited viremia.

There are only two trials of monotherapy with DRV/r[26,27], but they are the largest randomized trials of simplifying to monotherapy. The MONET trial[26] included 256 patients with HIV RNA < 50 copies/ml for over 24 weeks on NNRTI-based (43%), or PI-based (57%) antiretroviral therapy. Patients were naive to DRV, and they switched to DRV/r 800/100 mg once-daily, either as monotherapy or with two NRTI. In this study, all patients with two viral loads > 50 copies/ml were considered as failures, even if they reached again HIV RNA < 50 copies/ml with the same therapy or after restarting NRTI. In the primary efficacy analysis, the percentage of patients with HIV RNA < 50 copies/ml by week 48 (per protocol) was 86.2 vs. 87.8% in the monotherapy and triple therapy arms; by intent-to-treat (switch equals

failure), efficacy was 84.3 vs. 85.3%; by a switch-included analysis, efficacy was 93.5 vs. 95.1%; all three comparisons and all the other performed sensitivity analyses showed non-inferior efficacy for DRV/r monotherapy. Of note, this is the first study of monotherapy showing non-inferiority in all the analyses, including "as-treated" analysis and considering those patients who restarted NRTI as failures.

Only one patient per arm showed some PI mutation associated to resistance, but none of them had decreased susceptibility to DRV, and both reached again HIV RNA < 50 copies/ml without a change of their therapy.

The MONOI trial[27] randomized 226 patients to DRV/r 600/100 mg twice-daily, either as monotherapy or with two NRTI. Its inclusion criteria was somewhat different to other trials simplifying to monotherapy as it included patients with HIV RNA < 400 copies/ml in the last 18 months, and a result with < 50 copies/ml was only required at entry. The objective was to demonstrate non-inferiority of the monotherapy arm, but with an unusual criterion, using a non-inferiority margin of 10% of a confidence interval of 90%. In the per-protocol analysis at 48 weeks, the rate of virologic success of DRV monotherapy was 94.1% compared to 99% in the triple-therapy group, demonstrating non-inferiority (lower limit of CI = 9%). However, in the ITT analysis, the rate of success was 92% in the triple-therapy arm and 87.5% in the monotherapy arm. While the difference between the two arms was very consistent with a 4.5% difference, here the lower limit of CI was 11%, which does not allow assessing non-inferiority of the monotherapy arm.

In a sub-study of the MONOI trial performing serial dual energy X-ray absorptiometry (DEXA) scans on 141 patients[28], lipoatrophy was more frequent (11%) in the triple-drug arm compared to the monotherapy arm (1%), despite an NRTI backbone which included mainly non-thymidine analogs. At week 48, the switch to DRV/r monotherapy lead to a significant gain in limb fat tissue, contrasting with no change in the triple-drug arm.

Four studies have utilized ATV/r for simplification to monotherapy[29-32]. None of them was comparative, and the results are conflicting. In the largest study[32], 61 patients were simplified to ATV/r monotherapy. At 48 weeks, 67% of the patients maintained HIV RNA < 50 copies/ml in the ITT analysis. Of note, two patients (one of them after week 48) developed mutation 88S. This mutation has been related to ATV resistance, although viruses with this mutation retain susceptibility to other PI and could be easily treated.

Are all boosted protease inhibitors equal when used as monotherapy?

There are no comparative studies to date to answer this question. The design and endpoints of different studies on monotherapy are diverse and heterogeneous and it is not possible to obtain formal conclusions (Table 1 and 2). Darunavir/r has the best intratrial results, showing non-inferior efficacy versus triple therapy in all the performed analyses. It has also the added advantage of once-daily dosing and somewhat better tolerance. Lopinavir/r has shown non-inferiority compared to triple therapy, but only when it was evaluated as a strategy including reintroduction of NRTI if monotherapy did not maintain the virologic suppression. Lopinavir/r is the PI with the largest cumulative experience when used as monotherapy. Lopinavir/r in tablet form is currently the best option if refrigerator storage of ritonavir is an issue. Atazanavir/r has only been tested in small non-comparative trials. The efficacy rates with ATV/r seem somewhat lower than those reported in other trials with LPV/r or DRV/r, but the absence of a comparator does not allow confirmation of that insight. There is no published data about the use of fosamprenavir/ritonavir, saquinavir/ritonavir, or tipranavir/ritonavir in monotherapy.

Is boosted protease inhibitor monotherapy a risky option?

Several concerns are argued against implementing boosted PI monotherapy as a therapeutic option: the risk of development of resistance, the implications of the low-level viremia with these regimens, and the ability of monotherapy to control virus replication in anatomic reservoirs.

Resistance does not seem an actual problem when boosted PI monotherapy is used in simplification of virologically suppressed patients. In this scenario, the rate of development of PI resistance is low and it is similar to the rate of resistance with triple therapy in the comparative clinical trials. The incidence of resistance (0.5 per 100 patient-years of follow-up in the OK trials)[21] is lower than the incidence described with other well established strategies of simplification, such as those simplifying to efavirenz, nevirapine, or raltegravir[1]. Moreover, the therapeutic implications of resistance are also lower, as rescue remains possible with other drugs of the same family (PI) in all the reported cases, and no other family of antiretrovirals is involved, something not always true after simplification to NNRTI.

Table 1. Principal endpoints in the main clinical trials simplifying to boosted protease inhibitor monotherapy

OK pilot Trial[8] (LPV/r monotherapy)	Proportion of patients with < 500 copies/ml of HIV RNA of plasma at 48 weeks (intent to treat analysis).
OK-04[19] (LPV/r monotherapy)	Proportion of patients without therapeutic failure at 48 weeks: defined as two consecutive plasma HIV-1 RNA measurements ≥ 500 copies/ml. Re-induction with NRTI ≠ failure; change of randomized therapy or NRTI = failure.
KALMO[22] (LPV/r monotherapy)	Viral load < 80 copies/ml by week 48 (intent-to-treat analysis).
ACTG-5201[29] (ATV/r monotherapy)	Virologic failure, defined as two consecutive plasma HIV-1 RNA measurements of ≥ 200 copies/ml at or before 24 weeks.
OREY[32] (ATV/r monotherapy)	The proportion of subjects with virologic rebound (HIV RNA ≥ 400 copies/ml) or treatment discontinuation through week 48.
MONET[26] (DRV/r once-daily monotherapy)	Proportion of patients with treatment failure: two consecutive HIV RNA levels > 50 copies/ml at week 48, or discontinuation of randomized treatment (time to loss of virologic response) = failure; change of NRTI in the triple therapy arm ≠ failure (per protocol population).
MONOI[27] (DRV/r twice-daily monotherapy)	Proportion of patients with virologic failure: two consecutive HIV-1 RNA > 400 copies/ml within two weeks, or any therapy modification or study withdrawal (per protocol population).

LPV: lopinavir; /r: ritonavir boosted; ATV: atazanavir; DRV: darunavir; NRTI: nucleoside reverse transcriptase inhibitor.

The risk of resistance, however, could be higher when using monotherapy to treat naive patients[13] (especially in those with high viral loads), in monotherapy with LPV/r dosed once-daily[25], if low-level replication is maintained for long periods of time, and perhaps, in monotherapy with ATV/r[32], although there are no comparative studies to confirm this view. Special caution must be taken if monotherapy is prescribed in any of these situations.

Most of the virologic failures with monotherapy are due to confirmed low-level viremia (between 50 and 200-500 copies/ml), and this phenomenon is more frequent with boosted PI monotherapy than with triple therapy. The clinical implications of detectable viral loads between 50 and 200 copies are not clear and this subject is controversial. The American AIDS Clinical Trials Group (ACTG) uses an HIV RNA level of 200 copies/ml as the main virologic endpoint in their

Table 2. Principal conclusions of the main clinical trials simplifying to boosted protease inhibitor monotherapy

OK pilot Trial[8] (LPV/r monotherapy)	Most of the patients maintained with LPV/r monotherapy remain with undetectable viral load after 48 weeks.
OK-04[19] (LPV/r monotherapy)	48 weeks of LPV/r monotherapy with reintroduction of NNRTI as needed was non-inferior to continuation of two NNRTI and LPV/r in patients with prior stable suppression.
KALMO[22] (LPV/r monotherapy)	Switching to LPV/r monotherapy was effective, safe, and well tolerated.
ACTG-5201[29] (ATV/r monotherapy)	Simplified maintenance therapy with ATV/r alone may be efficacious for maintaining virologic suppression in carefully selected patients with HIV infection.
OREY[32] (ATV/r monotherapy)	Most subjects maintained virologic suppression after switching to once-daily ATV/r monotherapy.
MONET[26] (DRV/r once-daily monotherapy)	The DRV/r arm showed non-inferior efficacy versus the control arm in the primary efficacy analysis.
MONOI[27] (DRV/r twice-daily monotherapy)	DRV/r monotherapy showed non-inferior efficacy versus two NRTI + DRV/r at week 48 in the primary analysis.

LPV: lopinavir; /r: ritonavir boosted; ATV: atazanavir; DRV: darunavir; NNRTI: nonnucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor

trials as it was felt that this was the lowest threshold at which assay variation would not lead to random positive values[33]. The US Department of Health and Human Services panel on Antiretroviral Guidelines for Adults and Adolescents affirm in their last document that "persistent low-level viremia (e.g. HIV RNA 50-200 copies/ml) does not necessarily indicate virologic failure or a reason to change treatment"[1]. However, it does not seem reasonable to maintain monotherapy if there is persistent low-level HIV replication, as this could be a risk factor to develop resistance. In the OK04 trial[20], the protocol was amended after the first year of follow-up to recommend restarting NRTI if low-level viral load was confirmed in three consecutive samples over a two-month period. Even though no genotypic resistance test could be done in these cases, the viral load was re-suppressed to < 50 copies/ml in all the cases and no new mutations emerged after that change. Also, in the MONET trial, NRTI were added back to four of the 11 patients with confirmed HIV RNA elevations while on DRV/r monotherapy, and all of them suppressed their viral load to < 50 copies/ml, and another four of those 11 patients with virologic failure reached undetectable HIV RNA while continuing monotherapy[26].

In our clinical practice, if a patient on monotherapy presents an HIV RNA between 50 and 200 copies/ml, we extract a new sample after 2-4 weeks. If the viral load remains in that range, we extract a third sample after another 2-4 weeks, and we restart triple therapy if the viral load is again > 50 copies/ml. Whatever the cause may be (bad adherence, interactions, lack of potency, etc.), this finding is an indicator that monotherapy is not suitable for that patient, and NRTI are added again to the regimen. If HIV RNA is > 200 copies/ml, we try to perform a genotypic test and if, as is usual, no resistance is found, we follow the same process.

It must be noted, however, that if HIV RNA is < 50 copies/ml, the grade of suppression of viral replication is the same with monotherapy as with triple therapy, as assessed with an ultrasensitive HIV RNA quantitative test[34].

Finally, the question about the activity of boosted PI monotherapy to control viral replication in anatomical reservoirs, mainly in the central nervous system (CNS), remains open, as well as the role of triple therapy to suppress viral replication in the CNS and to avoid neurocognitive impairment, which also remains currently open. Both LPV and DRV have good enough penetration in cerebrospinal fluid (CSF), but that could be insufficient[35]. Nevertheless, most patients on monotherapy in clinical trials whose CSF has been examined do not show detectable virus[24,36]. No special concern has arisen regarding neurocognitive impairment in those patients treated with monotherapy in clinical trials, some of them followed for more than four years[37], but no specific diagnostic tool was included in those trials. Some anecdotal cases of CNS impairment while taking boosted PI monotherapy have been reported, but similar cases have also been reported with triple therapies[38], and it is not known if the risk with monotherapy is higher or not. Therefore, this question has to be carefully followed in the next years.

When could boosted protease inhibitor monotherapy be prescribed?

With all the information generated in the last seven years, many experts consider that monotherapy cannot be currently recommended because it has been somewhat less effective in achieving complete virologic suppression[1,39]. Other groups of experts, such as those writing the European or the Spanish guidelines[2,40], consider that boosted PI monotherapy with twice-daily LPV/r or DRV/r once-daily might represent an option in patients with intolerance to NRTI or for treatment simplification. Such a strategy only applies to patients without a history of failure on prior PI-based therapy and who have had a viral load < 50 copies/ml in at least the past six months. From a clinical point of view, monotherapy could be tried with minimal risk for the patient if the above conditions apply and this will work in most patients, with the added value that it is possible to go back to the previous regimen if monotherapy is not enough to maintain suppressed levels of HIV RNA. In addition, this can be done with a cost that is about half of the price of standard triple therapy[41].

Costs could also be a factor to take into account when prescribing monotherapy in resource-limited settings. Using the price for Spain of the currently recommended NRTI combinations, if the actual difference in the percentage of patients who maintain < 50 copies/ml is 1% lower with monotherapy than with triple therapy (as seen in the MONET trial[26]), and we treat 100 patients with triple therapy during one year, the incremental cost for one more patient with < 50 copies/ml will be about 500,000 euros/year. Even in the worst scenario with an actual difference of 20% lower with monotherapy, the cost of every additional patient with < 50 copies/ml will be about 25,000 euros/year if triple therapy is prescribed to all patients. And this is absolutely relevant when we know that these additional

patients with > 50 copies/ml due to monotherapy can be easily re-suppressed with the same triple therapy.

Finally, even if we do not consider monotherapy as an actual therapeutic option, research on boosted PI monotherapy has given us the opportunity to know the real role of boosted PI in antiretroviral combinations better. This has taught us how to optimize antiretroviral therapy in different situations, using more rational combinations.

Conclusions

After more than seven years of research, simplification of a suppressive triple antiretroviral therapy to boosted PI monotherapy has demonstrated safety and efficacy in a high proportion of patients. Although this is not a strategy to implement indiscriminately in all patients, it could be a good option for those patients with toxicity related to NRTI or for trying to avoid such toxicities if two main conditions, according to most of the clinical trials, are considered: no history of previous virologic failure or major mutations of resistance while taking a PI, and maintained suppression to < 50 copies/ml for more than six months. If these premises are fulfilled, it is safe enough to try this strategy and re-start NRTI if the viral load does not remain undetectable, whatever the cause may be.

If simplification to monotherapy is selected to treat some patients, twice-daily LPV/r, or preferably once-daily DRV/r, has to be chosen as data with other boosted PI are inconclusive or even nonexistent.

Nevertheless, more studies focusing on the control of HIV replication in viral reservoirs with monotherapy, as with triple therapy, are warranted.

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