Farm Hosp. 2010;**34(5):**251–258

Farmacia
HOSPITALARIA

www.elsevier.es/farmhosp

REVIEW

Meta-analysis of the effectiveness of the strategy of monotherapy with boosted protease inhibitors in HIV+ patients

J. Saez de la Fuente, A. Such Díaz, C. Sánchez Gil, C. Esteban Alba, and I. Escobar Rodríguez*

Servicio de Farmacia, Hospital Infanta Leonor, Madrid, Spain

Received October 19, 2009; accepted January 20, 2010

KEYWORDS
HIV protease inhibitors;
Meta-analysis;
Boosted ritonavir;
Lopinavir;
Darunavir;
Ritonavir

Abstract
Introduction: The objective of this study is to analyse the available evidence regarding the effectiveness of the strategy of induction maintenance with boosted protease inhibitors with ritonavir in adult HIV patients as compared to conventional treatment.
Methods: We performed a meta-analysis of randomised controlled trials in HIV patients to compare the efficacy of a monotherapy strategy of boosted protease inhibitors as compared with conventional antiretroviral therapy. The literature search was conducted in PubMed, EMBASE (September 1999-September 2009) and in conference abstracts of the last 5 years. The Odds Ratio of treatment failure and their 95% confidence intervals were calculated. To combine the results of individual studies selected, a fixed effects model based on the Mantel-Haenszel method or random effects was used, depending on whether or not the results were heterogeneous.
Results: Initially a total of 1510 publications were found, of which just 8 studies met the criteria for inclusion in the meta-analysis. The combined Odds Ratio of the 8 studies is 1.39 (95% CI 1.02-1.90) for the treatment group with conventional antiretroviral treatment, but with a confidence interval close to the limits of statistical non-significance.
Conclusion: The results of the combined effectiveness analysis in the meta-analysis found no significant differences between the conventional strategy and monotherapy. This strategy is considered recommended (level A evidence) in patients with no history of previous failure of protease inhibitor, with undetectable plasma viral load and signs or symptoms of nucleoside/nucleotide toxicity.

*Corresponding author.
E-mail address: ismael.escobar@salud.madrid.org (I. Escobar Rodríguez).

1130-6343/ $ - see front matter

PALABRAS CLAVE
Inhibidores de proteasa;
Meta-análisis;
Ritonavir potenciado;
Lopinavir;
Darunavir;
Ritonavir

Meta-análisis sobre la eficacia de la estrategia de monoterapia con inhibidores de la proteasa potenciados en pacientes VIH+

Resumen
Introducción: El objetivo del presente trabajo es analizar la evidencia disponible sobre la eficacia de la estrategia de inducción mantenimiento con inhibidores de proteasa potenciados con ritonavir en pacientes adultos VIH respecto al tratamiento convencional.
Métodos: Se realizó un meta-análisis de ensayos aleatorizados y controlados en pacientes VIH para comparar la eficacia de una estrategia de monoterapia con inhibidores de proteasa potenciados frente al tratamiento antirretroviral convencional. La búsqueda bibliográfica se realizó en PubMed, EMBASE (septiembre 1999-septiembre 2009) y en resúmenes de congresos de los últimos 5 años. Se calcularon los Odds Ratio del fracaso terapéutico y sus intervalos de confianza del 95%. Para combinar los resultados de los estudios individuales seleccionados, se empleó un modelo de efectos fijos basado en el método de Mantel-Haenszel o de efectos aleatorios, en función de que exista o no heterogeneidad en los resultados.
Resultados: Se localizaron inicialmente un total de 1.510 publicaciones, de las que solo 8 estudios cumplieron los criterios de inclusión en el meta-análisis. El Odds Ratio combinado de los 8 estudios es de 1,39 (IC 95% 1,02-1,90) a favor del grupo de tratamiento con tratamiento antirretroviral convencional, pero con un intervalo de confianza cercano a los límites de la no significación estadística.
Conclusión: Los resultados del análisis de eficacia combinado en el meta-análisis no encuentran diferencias significativas entre la estrategia convencional y la monoterapia. Esta estrategia se considera recomendable (nivel A de evidencia) en pacientes sin historia de fracaso previo a inhibidores de la proteasa, con carga viral plasmática indetectable y signos o síntomas de toxicidad por análogos de nucleósidos/ nucleótidos.

Introduction

After over 20 years of clinical studies using antiretroviral drugs at every stage of human immunodeficiency virus (VIH) infection, either as monotherapy or in combinations of 2, 3 or more drugs, it has been clearly established that antiretroviral (ART) treatment with combinations of at least 3 drugs is the treatment of choice for HIV infection. There is solid evidence that this treatment strategy delays clinical progression, reduces hospital admissions and its associated costs, and significantly increases survival.[1]

Nevertheless, despite these unquestionable advantages, indefinite antiretroviral combination treatment creates a rigid therapeutic scenario with its own inherent problems. Firstly, adherence to ART plays a key role in the degree and duration of the antiviral response.[2] On the other hand, the appearance of resistance is an inevitable phenomenon when the HIV virus is exposed to the selective pressure exerted by drugs that fail to suppress viral replication.[3,4] Lastly, the toxicity of antiretroviral drugs in the medium and long term is also a limiting factor which obliges us to seek new therapeutic options that maintain the same antiviral potency.[5]

The current situation, therefore, is that a high percentage of patients who initiate antiretroviral treatment face the prospect of therapeutic failure (virological, immunological or clinical), which demands a rapid change of treatment in order to avoid mutations and an increase in plasma viral load. The goal of therapy is to reattain maximum viral supression by instating a new antiviral combination of two or three fully active drugs, in conjunction with other drugs which have already been used in the patient but which continue to show activity (resistance studies) and are well tolerated. This process of clinical evolution means that currently, despite having nearly 25 different antiretroviral drugs, each with a different mechanism of action (at the level of the viral replication cycle), at our disposal, there is still an overriding need to continue to look for new drugs that permit lasting viral replication control.

In contrast to this conventional way of using antiretroviral drugs, other strategies which are different, more dynamic and enable better adaptation of ART to the immunological status of the patient, achieving added advantages in terms of toxicity and ART adherence, have been tried.

One of the strategies which attempts to employ antiretroviral drugs in a different way is the so-called induction-maintenance strategy, which we can define as the use of antiretroviral medications in two different stages, which are applied sequentially: 1) an induction phase, which coincides with the start of ART and the aim of which is to obtain a virological response (undetectable plasma viral load),

minimizing the risk of resistance and encouraging rapid immune reconstitution and 2) a maintenance phase, in which, after achieving the induction phase objective, the ART is modified and simplified, reducing it to two or, preferibly, a single drug, but with the aim of maintaining the virological, immunological and clinical response.

In the history of antiretroviral treatment, the first clinical trials to investigate the possible efficacy of this strategies were patent failures[6-8] and they demonstrated that an induction-maintenance strategy cannot be applied using drugs with a low genetic (lamivudine) and/or pharmacokinetic barrier (nelfinavir and indinavir). The subsequent development of ritonavir-boosted protease inhibitors (PI) revived the hypothesis that monotherapy with one of these drugs (maintenance) could be enough to maintain control of viral replication effectively and safely, once such control had been achieved with a classic combination ART (induction).

Out of all the boosted PI, ritonavir-boosted lopinavir (LPV/r), with its high potency and high genetic and pharmacokinetic barriers, is the benchmark drug. Consequently, it was the best option for experimentally testing the monotherapy strategy. The recent incorporation of ritonavir-boosted darunavir (DRV/r) into clinical practice and the investigation of its use in the abovementioned strategy have also made it a suitable candidate for research purposes. The results of the clinical studies and trials which have been conducted to date have meant that, in the current antiretroviral treatment recommendations of the GESIDA group of experts and the National AIDS Plan,[1] simplification to lopinavir/ritonavir or darunavir/ritonavir monotherapy is considered a viable option in patients with no previous history of PI failure, an undetectable viral plasma load for 6 months and signs and symptoms of nucleoside/nucleotide analogue toxicity [level A recommendation (based on data from randomized and controlled studies)].

The success of this strategy and its inclusion as a treatment recommendation mean it is currently regarded as the only new treatment strategy which offers an alternative to indefinite, rigid ART, which can only be modified in cases of toxicity or therapeutic failure.

Consequently, the aim of this systematic review and meta-analysis is to analyze the available evidence on the efficacy of the PI-boosted monotherapy based strategy compared to conventional antiretroviral treatment in the HIV patient.

Methods

Selection criteria

A bibliographical search was made of randomized and controlled studies, in which a PI-boosted monotherapy strategy was compared with conventional ART. Studies in which information related to efficacy was available in the form of a publication or presentation at a congress were included in the analysis. The study selection criteria were as follows:

1) A randomized and controlled design
2) Minimum duration of the trial of 48 weeks
3) Virological efficacy cut-off point: a viral load of less than 50 copies/ml.

Information sources and search strategy

To identify relevant studies the PubMed and EMBASE databases were searched, using '*HIV protease inhibitors or ritonavir boosted and (HIV or HIV infections) and (monotherapy or single agent or single drug or alone or simplified) and humans*' as descriptors. The bibliographical search was conducted from September 1999 to September 2009.

In addition, the congress reports of the *Conference on Retroviruses and Opportunistic Infections* (CROI), the European AIDS Clinical Society and the International AIDS Society issued in the last 5 years were reviewed. A search was also made of information sources about the results of ongoing clinical trials which were available on the internet (www.cliniclatrials.gov).

Furthermore, relevant reviews and editorial articles published in major medical journals (AIDS, JAIDS, J Infect Dis, N Engl J Med, the Lancet) in the last year were identified and their content was examined to identify possible information about trials which might be of interest. In studies which were the subject of various publications, we used the data corresponding to the longest period of treatment.

We only selected articles which were published in English and Spanish.

Selection of studies

Three reviewers (SFJ, SDA and SGC) independently reviewed the information sources that were available, selecting studies in accordance with our previously defined inclusion and exclusion criteria. For the final selection the three reviewers had to reach a full consensus.

Study variables and population

The main variable for evaluating efficacy in the combined analysis was therapeutic failure. Efficacy was assessed by intention to treat (ITT) analysis and it included all the patients in each treatment regime who received at least one dose. Therapeutic failure was defined as cases with a VL>50 copies/ml and patients who abandoned the study for any reason or whose treatment was changed.

The target population for the study consisted of HIV-infected patients without any initial limitation that might compromise their inclusion in the meta-analysis, the only difference which was taken into account, in the sensitivity analysis, being whether patients were treatment-naive or had been previously treated. The conventional ART group, which received 2 or 3 antiretroviral drugs in combination, served as the control.

Statistical analysis

Odds Ratios (OR) and their 95% confidence intervals (CI) were calculated from tabulated data. In order to combine the results of selected individual studies a fixed effects model based on the Mantel-Haenszel or randomized effects method, depending on whether or not there was statistically signifi-

cant heterogeneity ($P<0.1$) in the results, was employed. To estimate and quantify heterogeneity amongst the different studies Cochran's Q statistic and the I statistic were employed,[2] so that 25%, 50% and 75% corresponded to low, moderate and high levels of heterogeneity, respectively.[9] The possible existence of publication bias[10] was evaluated visually by means of a funnel graph to contrast the effect of studies (OR) with their standard errors.[11] Finally, three sensitivity analyses were performed, repeating the combined analysis, firstly without studies with different inclusion criteria for patients, secondly eliminating the studies with the smallest sample sizes and finally separating studies, depending on the PI which was used. The statistical analysis was performed using the SPSS statistics® software (version 17.0) and the Review Manager software (version 5.0) (Cochrane Collaboration).

Results

Selection of studies and main characteristics

Initially a total of 1,510 publications were located but only 8 studies[12-19] met the meta-analysis inclusion criteria, as shown in Figure 1. A total of 1,071 patients, 577 (53.9%) in the monotherapy treatment group and 494 (46.1%) in the combination ART group, participated in the randomized and controlled trials (RCT) included in the meta-analysis. The data from the trial by Pulido et al[12] are included in the study by Arribas et al[13] because they are part of the same research study, which was published after 48 and then 96 weeks. The PI used in monotherapy during the maintenance phase was lopinavir/ritonavir in six[12-17] and darunavir/ ritonavir in two of the studies.[18,19]

The main characteristics and inclusion criteria for these trials are summarized in table 1. The chief differences in study design are: different duration of the treatment, ranging from 48 to 96 weeks, different baseline characteristics of patients when they were included in the trial and, finally, whether or not there was an ART induction treatment phase, and its duration, prior to patients being randomized to receive monotherapy. If the induction period is taken into account, only Delfraissy et al's study[14] includes treatment-naive patients with no previous ART induction treatment.

Analysis of efficacy

The therapeutic failure ORs for the different studies are shown in Figure 2. Statistical significance is not reached in any of the studies, there being a wide dispersion in the confidence interval in the studies by Arribas et al[15] and Nunes et al,[16] owing to their small sample size. The statistical analysis of heterogeneity was not significant (Figure 2), so the Mantel-Haenszel method was used. The combined OR for the 8 studies is 1.39 (CI 95% 1.02-1.90) and it is biased in favour of the conventional ART treatment group, but with a confidence interval close to the limits of statistical non-significance.

Sensitivity analysis

Three sensitivity analyses were performed to evaluate the validity of the results.

- In the first analysis the study by Delfraissy et al[14] was ruled out, as it was the only one which included patients who had received no previous treatment. The weighted OR is 1.37 (CI 95% 0.98-1.92), which falls outside of the limit of statistical significance and the heterogeneity analysis is not significant.
- In the second sensitivity analysis the studies with the smallest sample sizes were ruled out.[15,16] The weighted OR is 1.32 (CI 95% 0.96-1.83) and the analysis of heterogeneity between samples is not significant.
- Finally, the studies were separated according to the PI which was used in monotherapy. A weighted OR of 1.27 (CI 95%0.74-2.17) was obtained for darunavir/ritonavir and an OR of 1.46 (CI 95%0.99-2.14) for lopinavir/ritonavir, the heterogeneity analyses proving non-significant in both cases.

Publication bias

The publication bias results in the funnel graph show a slightly asymmetrical distribution. This seems to indicate the possible existence of what is known as the 'small studies effect', which reflects a variation between the effect found in small studies in comparison to big studies (Figure 3). These studies with a smaller sample size,[15,16] which are dispersed throughout the graph, are the ones which were eliminated in the second sensitivity analysis.

Discussion

The combined efficacy analysis results in the meta-analysis failed to pick up significant differences between the con-

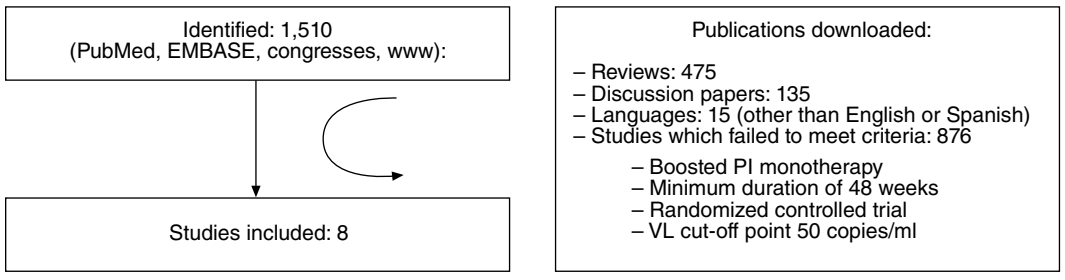

Figure 1 Selection of studies. PI indicates protease inhibitor; VL, viral load (copies/ml).

Table 2 Main characteristics of the studies included in the meta-analysis

Study	PI	HAART	Follow-up time	Initial patient status	Duration previous tt	Type of previous tt	Definition of ITT therapeutic failure	Mutation
Cameron et al[21]	LPV/r	3TC+AZT +EFV	96 weeks	Naive on inclusion VL>1,000 copies/ml After induction VL<50	No previous treatment Induction 6 months	None. After inclusion LPV/r, 3TC, AZT	>50 losses, interruptions, changes in tt	Resistance to PI in 3 monotherapy patients vs 1 HAART patient
Arribas et al (Pilot study OK)[19]	LPV/r	2 NRTI+ LPV /r or TDF+ NRTI+LPV/r	48 weeks	VL<50 copies/ml for 6 months	≥1 month	2 NRTI+LPV/r or TDF+NRTI+LPV/r	>50 losses, interruptions, changes in tt	Minor PI mutation in 1 monotherapy patient
Nunes et al[20]	LPV/r	NNRT+NRTI, PI+NRTI, 3 NRTI	96 weeks	VL<400 copies/ml for 6 months on inclusion VL<80 copies/ml	≥6 months	NNRTI+NRTI, PI+NRTI, 3 NRTI	>80 losses, changes in tt	No PI mutations
Delfraissy et al (MONARK)[18]	LPV/r	LPV/R+AZT +3TC	96 weeks	Naive VL<100,000 copies/ml	No previous treatment	None	>50, losses, interuptions, changes in tt	PI resistance mutations in 3 monotherapy patients vs 0 HAART patients Resistance to NRTI in 1 HAART patient vs 0 monotherapy patients
Pulido et al[16], Arribas et al[17] (OK)	LPV/r	2 NRTI+ LPV/r or TDF+NRTI +LPV/r	96 weeks	VL<50 copies/ml for 6 months	≥1 month	2NRTI+ LPV/r or TDF+NRTI+LPV/r	>50 losses, interruptions, changes in tt	Mutations which confer resistance to PI in 2 monotherapy patients
Arribas et al[22]	DRV/r	DRV+2 NRTI	48 weeks	VL<50 copies/ml for 6 months	7.4 years M-PI vs 6.4 years HAART	2 NRTI+NNRTI or boosted PI (not DRV)	>50 losses, interruptions, changes in tt	Genotype mutation to PI 1 monotherapy vs 1 HAART patient No phenotype resistance to DRV
Katlama et al[23]	DRV/r	DRV+2 NRTI	48 weeks	In the last 18 months VL<400 copies/ml On inclusion VL<50 copies/ml	≥18 months	No DRV (2 NRTI+PI, 3 NRTI, 2 NRTI+NNRTI)	>50 losses, interruptions, changes in tt	No mutations which confer resistance to DRV or PI in general

3TC indicates lamivudine; AZT, zidovudine; DRV/r, darunavir boosted with ritonavir; HAART, high-activity antiretroviral therapy; ITT, intention to treat; LPV/r, lopinavir boosted with ritonavir; M-PI, PI monotherapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; TDF, tenofovir; tt, treatment; VL, viral load (copies/ml).

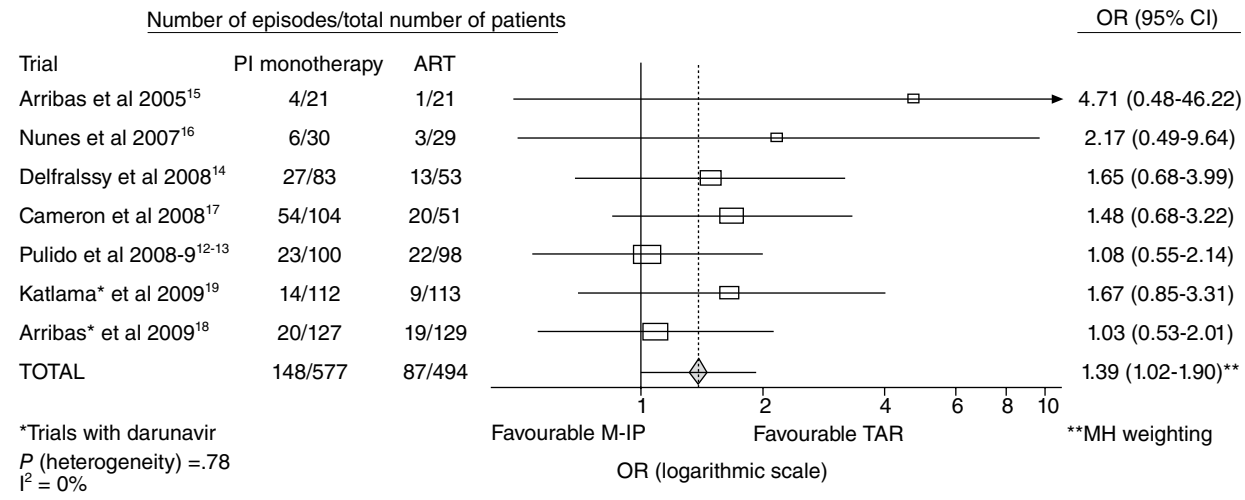

Figure 2 ITT analysis of the therapeutic failure variable. 95% CI indicates confidence interval 95%; ART,conventional antiretroviral treatment; M-PI, protease inhibitor monotherapy; MH, Mantel-Haenszel; OR, odds ratio; PI, protease inhibitor.

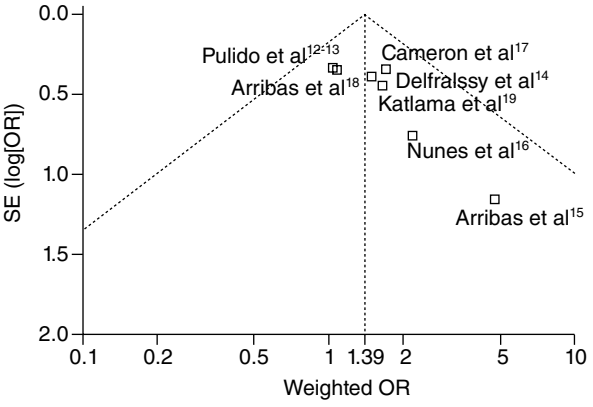

Figure 3 Funnel graph. Evaluation of publication bias representing the odds ratio of the different studies compared to their standard error (SE). The central line represents the adjusted OR and the lateral lines the 95% confidence interval. OR indicates odds ratio.

ventional strategy and monotherapy. The only difference is that the weighted OR is slightly higher, with a 95%CI, approximating the limits of non-significance, which became insignificant when the sensitivity analysis mentioned above was performed. The results of the analysis establish that both the strategy of simplification to LPV/r and to DRV/r manage to keep the PVL suppressed in a considerable number of patients and, in the case of LOP/r, for a long period of time.

This form of simplification has advantages in aspects related to clinical efficacy and safety, and also in terms of efficiency (cost/efficacy ratios).

With respect to efficacy, the only limitation worthy of mention is the greater incidence of low-grade viraemia (50-500 copies/ml) and this is only found in the studies using LOP/r. Therefore, this strategy is only recommended at present as an alternative for cases where there is toxicity or intolerance to adjunctive drugs.[1] All the studies show that the increase in CD4 lymphocytes is no lower in patients receiving LOP/r monotherapy than in patients who are maintained on standard triple therapy, so, in any event, this low-grade viraemia does not appear to affect the immunological recovery of these patients. Furthermore, in the majority of cases, this low level of viraemia was not associated with the appearance of resistance mutations. In the case of LOP/r, it does not seem that this low-grade viraemia is related to an insufficient pharmacological potency. Its origin is not entirely understood, but it appears that inadequate adherence could play an important role, more so than in patients receiving standard triple therapy, as the short half-life of LPV/r means that the failure to take a dose of medication in monotherapy patients poses a higher risk of viral rebound. Whatever the case, the validity of this strategy has also been confirmed in efficacy studies in clinical practice.[20]

The boosted PI monotherapy strategy has been criticized, owing to the fact that it may be responsible for a possible increase in the incidence of PI resistance found in the subgroup analysis of Delfraissy et al's study.[14,21] As we have already said above, this study is different to the rest in that it recruited naive patients, so its results cannot be regarded as equivalent to those of the other trials. Other analyses of subgroups in different studies show adherence to treatment to be the best predictor of virological response, followed by CD4 nadir levels below 100 cells/μl.[22,23] In our study we were unable to analyze PI resistance as a result of mutations, owing to the variations in the data presented in the studies, depending on their methodology. Some studies performed an analysis of resistance on all the patients who experienced therapeutic failure, while others only analysed an incom-

plete sample of cases of failure or they only analysed patients receiving monotherapy (Table).

With respect to safety, the studies have confirmed that the patients treated with LPV/r monotherapy improved their quality of life and had fewer adverse effects, one of which was lipodystrophy.[17,24]

With regard to efficiency, there are two advantages, which are unquestionably related in terms of costs: 1) the first is that, as the risk of the adverse effects of NRTI are reduced in the medium or long term, their associated costs are reduced and 2) the second is the reduction in the direct costs associated with ART. With respect to the former, in the study by Libre Codina et al,[25] calculating what the equivalent cost would be for our service, we quantified the total average costs due to adverse events associated with NRTI, over a period of 12 months, as 2,223 euros/year. Those which have the greatest economic impact are associated with lipoatrophy, mixed lipodystrophy and peripheral neuropathy. The supression of nucleoside analogues in an ART regime, in conjunction with viral replication control, would contribute to lowering these costs which are related to their toxicity. As far as the reduction of total direct costs is concerned, it is evident that a reduction in the number of drugs used for ART will result in a reduction in the final cost of treatment and the magnitude of the difference in both the pilot study and one or two clinical trials has been quantified.[26,27]

The limitations of the present study are the small number of RCT which have currently been published, the lack of homogeneity of their protocols, and the lack of data provided by the studies for resistance analysis, and other factors which facilitate the selection of subgroups of patients who would benefit most from this strategy.

To summarize, simplification to monotherapy, reintroducing drugs which are used in conjuntion with LPV/r in cases of viral rebound, has demonstrated a similar efficacy to combined treatment in clinical trials and in normal clinical practice. Lack of adherence is the factor which has the most influence on the virological failures that occur with this treatment regime. Should the same strategy be employed with DRV/r, its validity has been demonstrated in clinical trials, but specific studies which show its possible limitations, should there be any, and how to maintain its efficacy in the long term are needed.

References

1. Panel de expertos de Gesida y Plan Nacional sobre el Sida. Recomendaciones de Gesida/Plan Nacional sobre el Sida respecto al tratamiento antirretroviral en adultos infectados por el virus de la inmunodeficiencia humana (updated January 2010). 2009. [accessed 15/1/2010]. Available from: http://www.gesida.seimc.org/
2. Polo R, Knobel H, Escobar I. (Coordinators of PNS/SEFH/GESIDA expert). Mejorar la adherencia al tratamiento antirretroviral. Recomendaciones de la SPNS/SEFH/GESIDA. Farm Hosp. 2008;32:349-57.
3. Hammer SR, Eron JJ, Reiss P, Schooley RT, Thompson MA, Walmsley S, et al. Antiretroviral treatment of adult HIV infection: 2008 recommendations of the international AIDS Society USA-panel. JAMA. 2008;300:555-70.
4. Pannel of antiretroviral guidelines fotr adults and adolescents. Guideline for the use of antiretroviral agents in HIV-infected adults and adolescents. Department of Health and Human Services. January 29, 2008 [accessed 15/11/2009]. Available from: http://AIDSInfo.nih.gov/
5. Carr A, Cooper DA. Adverse effects of antiretroviral therapy. Lancet. 2000;356:1423-30.
6. Havlir DV, Marschner IC, Hirsch MS, Collier AC, Tebas P, Bassett RL, et al; AIDS Clinical Trials Group Study 343 Team. Maintenance antiretroviral therapies in HIV infected patients with undetectable plasma HIV RNA after triple-drug therapy. N Engl J Med. 1998;339:1261-8.
7. 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;16:561-8.
8. 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;352:185-90.
9. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-60.
10. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol. 2000;53:1119-29.
11. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J Clin Epidemiol. 2001;54:1046-55.
12. Pulido F, Arribas J, Delgado R, Cabrero E, González-García J, Pérez-Elias MJ, et al. Lopinavir-ritonavir monotherapy versus lopinavir-ritonavir and two nucleosides for maintenance therapy of HIV. AIDS. 2008;22:F1-9.
13. Arribas JR, Delgado R, Arranz A, Muñoz R, Portilla J, Pasquau J, et al. Lopinavir–ritonavir monotherapy versus lopinavir–ritonavir and 2 nucleosides for maintenance therapy of HIV: 96-week analysis. J Acquir Immune Defic Syndr. 2009;51:147-52.
14. Delfraissy JF, Flandre P, Delaugerre C, Ghosn J, Horban A, Girard PM, et al. Lopinavir/ritonavir monotherapy or plus zidovudine and lamivudine in antiretroviral-naive HIV-infected patients. AIDS. 2008;22:385-93.
15. 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;40:280-7.
16. Nunes EP, Oliveira MS, Almeida MMTB, Pilotto JH, Ribeiro JE, Faulhaber JC, et al. 96-week efficacy and safety results of simplification to single agent lopinavir/ritonavir (LPV/r) regimen in patient suppressed below 80 copies/mL on HAART–the KalMoStudy. 11th European AIDS Conference, European AIDS Clinical Society, 2007: Madrid, Spain. Abstract P75/04.
17. Cameron DW, Da Silva BA, Arribas JR, Myers RA, Bellos NC, Gilmore N, et al. A 96-week comparison of lopinavir-ritonavir combination therapy followed by lopinavir-ritonavir monotherapy versus efavirenz combination therapy. J Infect Dis. 2008;198:234-40.
18. Arribas JR, Horban A, Gerstoft J, Fätkenheuer G, Nelson M, Clumeck N, et al. The MONET trial: darunavir/ritonavir monotherapy shows non-inferior efficacy to standard HAART, for patients with HIV RNA<50 copies/mL at baseline. In: V IAS Conference; Cape Town, South Africa; July 19-22, 2009. Abstract TUAB106-LB.
19. Katlama C, Valantin MA, Algarte-Genin M, Duvivier C, Lambert-Niclot S, Girard GR, et al. A randomized multicenter study to compare the efficacy of a monotherapy of darunavir to a triple therapy with 2 nucleosides analogues combined to darunavir/r

in HIV infected patients with full viral suppression. In: V IAS Conference; Cape Town, Soth Africa; Juy 19-22, 2009. Abstract WELBB102.
20. Molto J, Santos JR, Negredo E, Miranda C, Videla S, Clotet B. Lopinavir/ritonavir monotherapy as a simplification strategy in routine clinical practice. J Antimicrob Chemother. 2007;60:436-9.
21. Delaugerre C, Flandre P, Chaix ML, Ghosn J, Raffi F, Dellamonica P, et al. Protease inhibitor resistance analysis in the MONARK trial comparing first-line lopinavir-ritonavir monotherapy to lopinavir-ritonavir plus zidovudine and lamivudine triple therapy. Antimicrob Agents Chemother. 2009;53:2934-9.
22. Pulido F, Pérez-Valero I, Delgado R, Arranz A, Pasquau J, Portilla J, et al. Risk factors for loss of virological suppression in patients receiving lopinavir/ritonavir monotherapy for maintenance of HIV suppression. Antivir Ther. 2009;14:195-201.
23. Campo RE, Da SIva BA, Cotte L, Gathe JC, Gazzard B, Hicks CB, et al. Predictors of loss of virologic response in subjects who simplified to lopinavir/ritonavir monotherapy from lopinavir/ritonavir plus zidovudine/lamivudine. AIDS Res Hum Retroviruses. 2009;25:269-75.
24. Spire B, Marcellin F, Cohen-Codar I, Flandre P, Boue F, Dellamonica P, et al. Effect of lopinavir/ritonavir monotherapy on quality of life and self-reported symptoms among antiretroviral-naive patients: results of the MONARK trial. Antivir Ther. 2008;13:591-9.
25. Libre Codina JM, Casado Gómez MA, Sánchez de la Rosa R, Pérez Elías MJ, Santos González J, Miralles Álvarez C, et al. Costes de la toxicidad asociada a los análogos de nucleósidos inhibidores de la transcriptasa inversa en pacientes con infección por el VIH-1. Enferm Infecc Microbiol Clin. 2007;25:98-107.
26. Escobar I, Pulido F, Pérez E, Arribas JR, García MP, Hernández A. Análisis farmacoeconómico de una estrategia de mantenimiento con lopinavir/ritonavir como monoterapia en pacientes con infección por el VIH. Enferm Infecc Microbiol Clin. 2006;24:490-4.
27. Arribas JR, Pulido F, Méndez I, Lázaro P, Norton M, Cabrero E, et al. 96 wks pharmacoeconomic outcome of lopinavir/r monotherapy as maintenance strategy in HIV+ patients with suppressed viral load. OK04-PharmECO analysis. 9th International Congress on Drug Therapy in HIV Infection. Glasgow, November 9-13, 2008 [abstract P308].