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Similar antiviral efficacy and tolerability between efavirenz and lopinavir/ritonavir, administered with abacavir/lamivudine (Kivexa®), in antiretroviral-naïve patients: A 48-week, multicentre, randomized study (Lake Study)

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ABSTRACT

Background: Although efavirenz and lopinavir/ritonavir(r) are both recommended antiretroviral agents in antiretroviral-naïve HIV-infected patients, there are few randomized comparisons of their efficacy and tolerability.
Methods: A multicenter and randomized study was performed including 126 antiretroviral-naïve patients, randomly assigned to efavirenz + Kivexa® ($n = 63$) or lopinavir/r + Kivexa® ($n = 63$). Efficacy endpoints were the percentage of patients with HIV-RNA $\leq$50 copies/mL at week 48 and CD4 recovery. Safety was assessed by comparing toxicity and discontinuations. Statistical analyses were performed on an intention-to-treat (ITT) basis (Missing = Failure).
Results: At week 48, 56.7% of patients in the efavirenz and 63.2% in the lopinavir/r groups showed HIV-1 RNA <50 copies/mL ($P = 0.770$) (intention-to-treat analysis; Missing = Failure). Only 1 (1.53%) patient from each group experienced virological failure. CD4 values increased in both groups (298 cells in the efavirenz group, $P = 0.001$; 249 cells in the lopinavir/r group, $P = 0.002$; $P = 0.126$ between groups). HDL-cholesterol only increased in the efavirenz group (from 39 ± 12 mg/dL to 49 ± 11; $P = 0.001$). Discontinuations were more frequent in the lopinavir/r group (36.5% versus 28.5%; $P = 0.193$), but more patients with efavirenz interrupted due to toxicity (11.1% versus 6.3%); most of them were attributed to hypersensitivity reaction.
Conclusions: Similar virological efficacy was observed for efavirenz and lopinavir/r, when administered with Kivexa® in antiretroviral-naïve patients, while immunological improvement was slightly superior for efavirenz. The higher rate of discontinuation due to toxicity in the efavirenz group was related to a higher incidence of hypersensitivity reaction. Nowadays, the use of the new formulation of lopinavir/r and the HLA-B*5701 genotype test before starting abacavir should improve the safety profiles of these regimens.

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1. Introduction

The introduction of highly active antiretroviral therapy (HAART) has profoundly altered both the course and prognosis of HIV-infection. After 1996, the availability of protease inhibitors (PI) transformed HIV-infection from a progressive and almost uniformly fatal condition to a treatable chronic infection.

Choosing an initial antiretroviral regimen is one of the most important decisions faced by clinicians managing HIV disease. Several antiretroviral combinations have proven sufficiently potent to achieve viral suppression in most treated patients. However, maintaining efficacy depends on other factors, such as the durability of antiviral suppression, tolerability, risk of long-term toxicity, and patient convenience. Based on these considerations and on the results of several trials (Allavena et al., 2005; De luca et al., 2006), international treatment guidelines recommend regimens containing two nucleoside reverse transcriptase inhibitors (NRTIs) and a ritonavir-boosted PI or a non-nucleoside reverse transcriptase inhibitor (NNRTI) in treatment-naïve patients. More specifically, the 2008 European guidelines for antiretroviral management consider a regimen based on lopinavir/ritonavir (lopinavir/r) or efavirenz to be one of the first-line choices for HIV-infected antiretroviral-naïve patients (EACS, 2008).

To date, lopinavir/r is one of the PIs of choice because of its high antiviral potency, long durability, low risk of resistance, and its acceptable tolerance. Efavirenz is the recommended NNRTI because of its low pill burden, which makes adherence easier, and the high number of patients who achieve viral suppression (EACS, 2008). In addition, combinations based on efavirenz and boosted PIs have shown favourable immunological and clinical outcomes in deeply immunosuppressed antiretroviral-naïve HIV-1-infected patients (Domingo et al., 2008; Tashima et al., 2008; Pulido et al., 2004; Arribas et al., 2002).

However, the number of subjects maintaining viral suppression 1 year after starting triple therapy probably decreases when we consider patients outside clinical trials. Most of the patients who experience virological failure will be able to re-establish viral control with a subsequent regimen, although viral suppression can be progressively more difficult to achieve and the accumulation of mutations reduces the number of future therapeutic options. Therefore, it is important to monitor those factors that predict response to treatment from the outset, particularly the complexity of the regimen and tolerability, both of which are associated with long-term adherence (Tashima et al., 2008).

Published data have directly compared efavirenz and lopinavir/r in antiretroviral-naïve patients (Allavena et al., 2005; De luca et al., 2006; Domingo et al., 2008; Tashima et al., 2008; Pulido et al., 2004; Bartlett et al., 2001; Manfredi et al., 2004; Riddler et al., 2008; Torti et al., 2005), but the controversies arising from recent results on efavirenz and lopinavir/r should be addressed by analyzing virological outcome, resistance, and long-term toxicity with these agents (Riddler et al., 2008).

We designed a head-to-head randomized study to evaluate the long-term efficacy and safety of two potent antiretroviral combinations composed of efavirenz or lopinavir/r plus abacavir/lamivudine (Kivexa®) in antiretroviral-naïve patients.

2. Methods

2.1. Study design and participants

This was a prospective randomized multicenter study with 48 weeks of follow-up conducted in 19 centers in Spain (18) and Italy (1) (NCT00318123). The inclusion period was from March 2005 to March 2006.

To be included, patients had to be HIV-1-infected, aged 18 years or above, antitretroviral-naïve, with no history of a recent opportunistic infection (<4 weeks) or immunomodulating agents before baseline.

The institutional review board at each site approved the study and all the patients provided written informed consent before screening.

2.2. Randomization, follow-up, and assessment

Patients were randomly assigned in a ratio of 1:1 to receive oral treatment with efavirenz (EFV) (600 mg) + abacavir (600 mg)/lamivudine (300 mg) (Kivexa®) once daily (efavirenz group) or lopinavir (400 mg, 3 capsules)/ritonavir (100 mg) twice daily plus Kivexa® once daily (lopinavir/r group). HLA-B*5701 test was not determined at baseline (genetic test was not easily available at that time).

Patients were assessed at week 4 and every 3 months thereafter until week 48 for virological and immunological response. Viral suppression was defined as a plasma viral load of less than 50 copies/mL. Virological failure was defined as the non-achievement of viral suppression at week 24 (viral load >50 copies/mL) or if, during the follow-up, a patient who had previously achieved viral suppression presented a confirmed viral load above ≥50 copies/mL. HIV-RNA was determined using the AMPLICOR HIV-1 MONITOR Test, v 1.5 (Roche Diagnostic, Basel, Switzerland).

Lipid and hepatic changes, adverse reactions, and reasons for discontinuation were also recorded at the same time points to assess safety. The lipid profile included determination of total, LDL-, and HDL-cholesterol and triglyceride levels, and liver function testing included transaminase levels (aspartate aminotransferase and alanine aminotransferase). Changes in body fat distribution were recorded by questionnaire self-report throughout the 48 weeks of the study, as was the severity of these changes.

Adverse events were classified according to the definitions of the World Health Organization (WHO). Reasons for discontinuation were classified as follows: virological failure, adverse events (grades I and II or III and IV), hypersensitivity reaction, death, or any other cause (voluntary discontinuation, simplification, etc.).

2.3. Outcome measures

The primary efficacy endpoint was the percentage of responders, that is, a patient who completed 48 weeks of study with the assigned treatment and maintained a viral load ≤50 copies/mL.

The secondary efficacy endpoints were the percentage of patients who experienced a virological failure and changes in CD4 cell count at week 48.

The percentage of patients with a viral load of less than 50 copies/mL at week 48 was also analyzed depending on whether the baseline CD4 cell count was greater or less than 200 cells/μL or whether viral load was greater or less than 100,000 copies/mL.

The proportion of patients who achieved a CD4 cell count ≥200 cells/μL at week 48 was analyzed in those patients who showed a baseline CD4 cell count below 200 cells/μL and did not experience virological failure.

Changes in lipid and hepatic parameters at week 48 from baseline, the percentage of patients with serious (grades III and IV) adverse events, and the percentage of patients who discontinued the study throughout 48 weeks of follow-up were safety endpoints.

The time to treatment failure, defined as time to virological failure or treatment discontinuation for any reason, was also compared between both regimens.

Table 1
Baseline patient and HIV-related characteristics.

Characteristics	Efavirenz ($n=63$)	Lopinavir/r ($n=63$)
Age (years)[a]	39 (±8.45)	37 (±9.41)
Gender (male) (%)	86	86.8
CDC category C (%)	7.3	7.7
CD4 cells count/μL[a]	193 (±122)	191 (±127)
CD4 <200 cells/μL (%)	42.8	38.1
CD4 cells count/μL nadir[a]	136 (±248.5)	211 (±272)
Viral load (copies log/mL)[a]	258,528 (±741,163)	194,524 (±286,979)
Viral load >100,000 copies/mL (%)	38.1	39.7
Risk behavior (%)		
Homosexual relations	47.3	38.9
Lipid profile		
Total cholesterol (mg/dL)[a]	157 (±35)	149 (±31.6)
HDL-cholesterol (mg/dL)[a]	39 (±11.5)	41 (±29.7)
LDL-cholesterol (mg/dL)[a]	94 (±33)	97 (±22.4)
Transaminases		
AST (U/L)[a]	33 (±20.4)	37 (±29.7)
ALT (U/L)[a]	33 (±26.3)	47 (±51.1)

ALT, aspartate aminotransferase; AST, aspartate aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a] Expressed as mean (±SD).

2.4. Statistical analysis

The sample size was calculated with 78% power and 95% confidence to demonstrate equivalence between treatments considering an equivalence range of 0.2. The proportion of patients with undetectable viral load was estimated from previous studies to be 0.8. To allow for a 5% of lost of follow-up, a total of 126 patients were evaluated, the patients were equally allocated in the treatment groups.

The summary of quantitative variables was expressed either as the mean and standard deviation or as the median and interquartile range (IQR); frequencies and percentages were given for the qualitative variables.

The continuous variables were compared with Student's *t*-test for variables with a normal distribution and with the Mann–Whitney *U*-test for variables with an abnormal distribution. To assess significance in changes observed over time the Wilcoxon signed rank test was performed. For discrete variables, Chi-Square or Fisher's exact tests (as appropriate) were used.

Patients who were lost during follow-up were excluded from the on-treatment analysis; for the main outcome an intention-to-treat analysis was performed, considering Missing = Failure.

Distribution of values for time to treatment failure was assessed using the survival curves by Kaplan–Meier's method. Difference between curves was evaluated by means of the log-rank test.

Statistical analysis was performed with the SPSS 15.0 program (SPSS, Inc., Chicago IL, USA).

3. Results

Of the 126 antiretroviral-naïve patients who underwent randomization, 63 were assigned to the efavirenz group and 63 to the lopinavir/r group.

No significant differences in epidemiological and HIV-related characteristics were seen between the groups (Table 1). Overall, 86.4% of patients were male and the median age was 37 ± 9 years. The most common route of HIV transmission was homosexual relations (43.1%) and the median time from HIV diagnosis was 20.9 ± 57.9 months. There were no differences between the groups for baseline CD4 cell count, viral load, or HIV clinical stage.

Fig. 1 shows the patients' enrollment and outcomes.

3.1. Virological outcome

The percentage of responders was similar between the two treatment groups, with no significant differences at week 48; the study was completed by 87% and 91.3% of patients with HIV-RNA < 50 copies/mL in the efavirenz and lopinavir/r groups, respectively ($P=0.382$) (OT analysis) (Fig. 2A). The proportions of patients with HIV-1 RNA < 50 copies/mL at week 48 in the intention-to-treat analysis (Missing = Failure) were 56.7% in the efavirenz group and 63.2% in the lopinavir/r group ($P=0.770$).

Only 1 (1.53%) patient from each group experienced virological failure. The patient from the efavirenz group failed at week 36 and genotyping revealed the K103N, V179E, and M184V mutations in the transcriptase gene and the L33I mutation in the protease gene. The patient from the lopinavir/r group showed a virological rebound at week 48 with the presence of M46L and L63P mutations in the protease gene with no mutations in the transcriptase gene.

The proportion of patients who achieved viral suppression was equal when we considered baseline CD4+ T-cell counts in subjects from the lopinavir/r group (66.7% for those with >200 cells/μL and 66.7% for those with <200 cells/μL achieved RNA-1 <50 copies/mL; $P=1.000$); in the efavirenz group, the proportion of subjects with RNA-1 <50 copies/mL was lower when patients started therapy while more severely immunosuppressed (75% for those with >200 cells/μL and 51.9% for those with <200 cells/μL, although these differences were not statistically significant ($P=0.074$) (Fig. 2B). Between groups, no statistically significant differences were found when subjects with baseline CD4+ T-cell counts <200 cells/μL ($P=0.276$) and >200 cells/μL were compared ($P=0.526$; ITT analysis).

The same was true when we compared the proportions considering baseline plasma viral load <100,000 copies/mL (56% in efavirenz and 72.2% in lopinavir/r groups achieved RNA-1 < 50 copies/mL, $P=0.263$) or >100,000 copies/mL (70.8% in the efavirenz group and 64% in the lopinavir/r group, $P=0.609$).

There was no significant difference in time to treatment failure between the efavirenz group (40.9 ± 2.04 weeks) and the lopinavir/r group (43.6 ± 1.85 weeks) ($P=0.491$) (Fig. 4).

3.2. Immunological outcome

Significant increases in CD4 cell counts over 48 weeks were seen for both study arms. In the efavirenz group, the CD4 cell count improved from 193 cells/μL (±122) to 491 (±244) ($P=0.001$) and, in lopinavir/r group, from 191 cells/μL (±127) to 440 (±240) ($P=0.002$), without significant difference between groups ($P=0.126$) (Fig. 3).

Considering the 51 patients (27 in the efavirenz group and 24 in the lopinavir/r group) who presented a CD4+ T-cell count <200 cells/μL at baseline, 60.7% (55.5% and 66.6%, respectively; $P=0.634$) achieved a CD4+ T-cell count >200 cells/μL at week 48 (Fig. 3).

3.3. Efficacy

There were no significant changes in liver enzymes in either group.

Regarding lipid metabolism, a significant increase in total cholesterol (from 157 ± 35 mg/dL to 205 ± 28, $P=0.001$) and HDL-cholesterol (from 39 ± 12 mg/dL to 49 ± 11, $P=0.001$) was observed in the efavirenz group, while only an increase in total cholesterol (from 149 ± 31 mg/dL to 193 ± 46, $P=0.001$) was seen in patients receiving lopinavir/r at week 48.

Overall, only one participant (0.79%, lopinavir/r group) notified clinically evident body fat changes (moderate lipodystrophy).

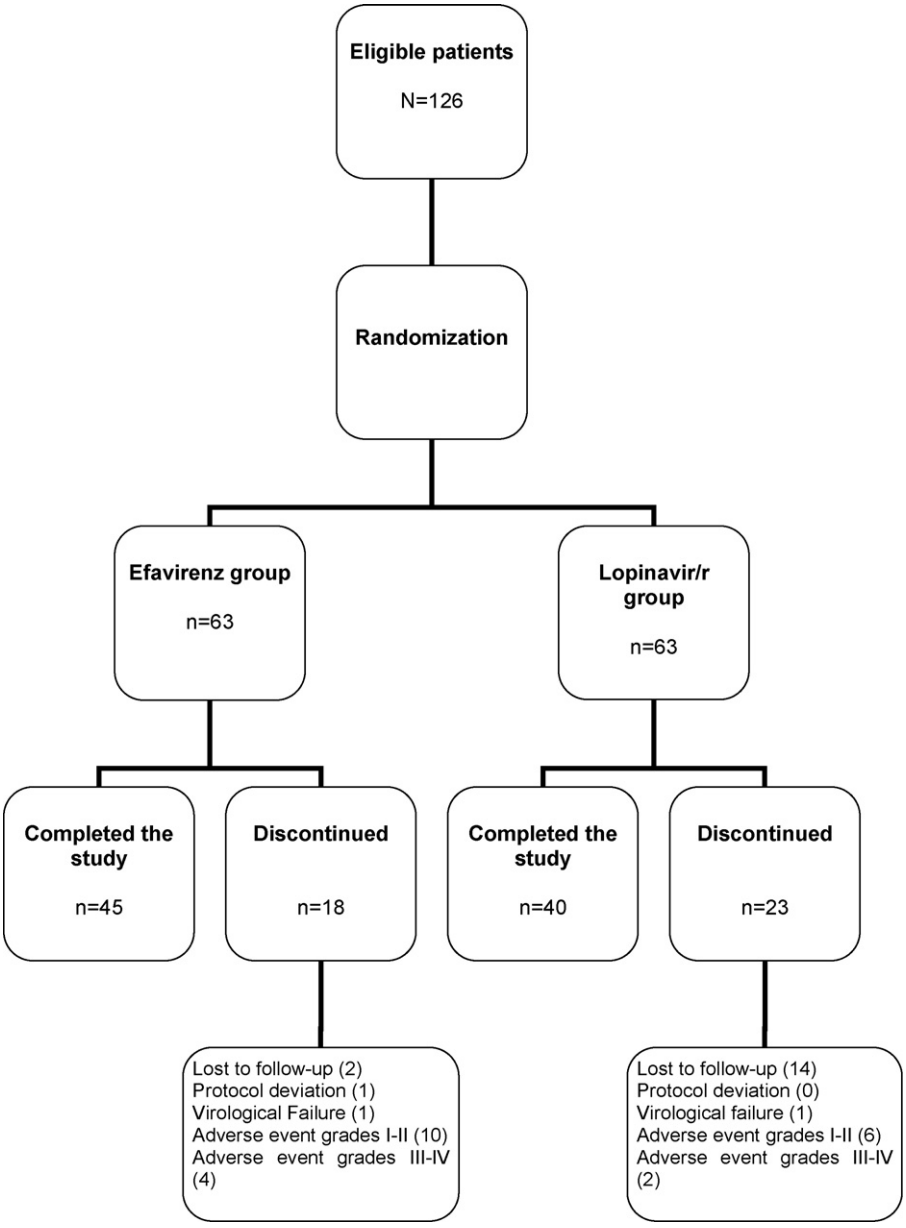


Fig. 1. Flow diagram showing the randomization process.

Treatment discontinuation occurred in 41 (32.5%) patients, 23 (36.5%) from lopinavir/r group and 18 (28.5%) from efavirenz group ($p = 0.193$). A total of 17.4% of participants discontinued the study by the emerging of adverse events: 14 subjects (11.1%) belonged to efavirenz group, 6 of them (42.8%) discontinued due to a hypersensitivity reaction/rash; 8 (6.3%) patients discontinued the study treatment due to toxicity in the lopinavir/r group, 2 due to hypersensitivity (Fig. 1). Adverse events occurred most frequently during the first 2 weeks of therapy.

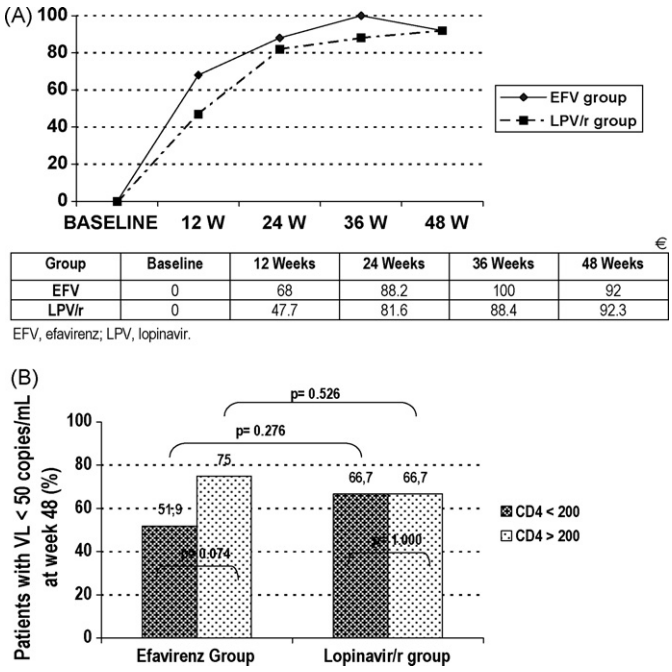
HLA-B*5701 genotype test was only retrospectively determined in four patients with hypersensitivity reaction from efavirenz group, being positive only in one case.

No deaths were reported during the study.

4. Discussion

Data comparing lopinavir/r- and efavirenz-based regimens are scarce and controversial, although both regimens are recommended as the first choice for initial antiretroviral therapy (De luca et al., 2006; EACS, 2008; Domingo et al., 2008). Therefore, this prospective and randomized study aimed to provide a head-to-head comparison to evaluate the efficacy and safety of two potent antiretroviral combinations based on efavirenz or lopinavir/r. Our results in 126 antiretroviral-naïve patients reveal comparable antiviral efficacy over 48 weeks for both agents when combined with abacavir/lamivudine (Kivexa®) as first-line antiretroviral regimens. However, although the rate of discontinuations was higher in patients receiving lopinavir/r, more patients from the efavirenz group discontinued therapy early due to adverse reactions, mostly hypersensitivity reactions.

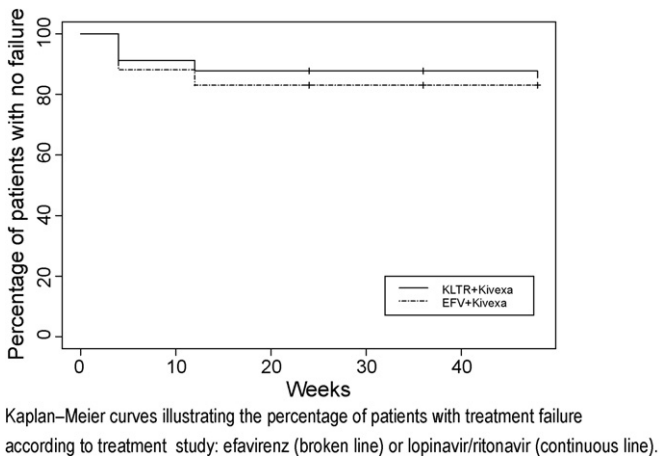
Virological data from studies comparing efavirenz or lopinavir/r with other strategies highlight their intrinsic potency, even in severely immunosuppressed subjects (Bartlett et al., 2007; Arribas et al., 2002). However, the ACTG 384 study was one of the first studies to demonstrate the superiority of efavirenz over a non-boosted PI (nelfinavir) in antiretroviral-naïve HIV-1-infected patients (Dubé et al., 2005). Later, other studies supported these results in similar populations with the same and other PIs (De luca et al., 2006;



Group	Baseline	12 Weeks	24 Weeks	36 Weeks	48 Weeks
EFV	0	68	88.2	100	92
LPV/r	0	47.7	81.6	88.4	92.3

EFV, efavirenz; LPV, lopinavir.

Fig. 2. Percentage of patients with VIH RNA <50 copies/mL during the study (on-treatment analysis). Percentage of patients with VIH RNA <50 copies/mL at week 48 according to the baseline CD4 cell count.



Kaplan–Meier curves illustrating the percentage of patients with treatment failure according to treatment study: efavirenz (broken line) or lopinavir/ritonavir (continuous line).

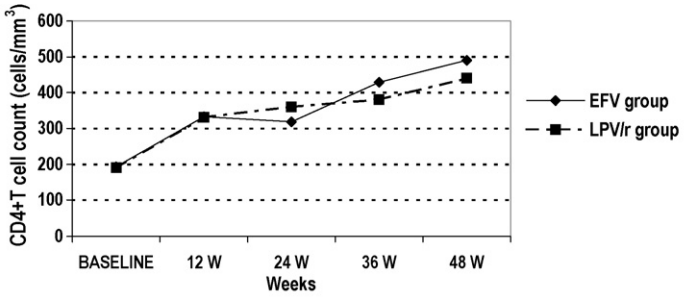
Fig. 4. Time to treatment failure. Kaplan–Meier curves illustrating the percentage of patients with treatment failure according to treatment study: efavirenz (broken line) or lopinavir/ritonavir (continuous line).

Domingo et al., 2008; Pulido et al., 2004; Manfredi et al., 2004; Friedl et al., 2001; Molina et al.). Nonetheless, all these studies compared efavirenz with a first-generation, non-ritonavir-boosted PI, such as indinavir, nelfinavir, or saquinavir, whose antiviral potency was shown to be lower than that of ritonavir-boosted PIs, specifically lopinavir/r. To date, only one recently published study (ACTG 5142) has directly compared efavirenz and lopinavir/r in a randomized trial (Riddler et al., 2008). The results at week 96 show a higher rate of virological response with efavirenz than lopinavir/r (89% versus 77%, $P = 0.003$), as well as a significantly longer time to virological failure and to treatment failure with efavirenz. The number of responders at 48 weeks of follow-up from our study was lower for both study drugs than those observed in ACTG 5142 at 96 weeks, probably because of our stricter statistical analysis (Missing = Failure) considering the relatively small group. In addition, it is noteworthy that our data do not support the superiority of efavirenz over lopinavir/r observed in ACTG 5142 with respect to virological response and time to regimen failure.

Data from the Castle study, which compared lopinavir/r with atazanavir/r, showed a lower virological response at week 96 with lopinavir/r when patients presented a poorer immunological status at baseline (Molina et al.). Our results do not show statistical differences between the drugs with respect to antiviral efficacy in more severely immunodepressed patients. In fact, the efavirenz-based regimen showed a less potent virological response in patients who were more immunosuppressed when they started therapy, though this was not statistically significant.

The results from ACTG 5142 showed a greater increase in CD4 cell count in the lopinavir/r group than in the efavirenz group ($P = 0.01$) at week 96, although there were no differences at week 48 (Riddler et al., 2008). A more pronounced, but not statistically significant, recovery in CD4 count was attained in the efavirenz-treated patients, whereas a slightly higher proportion of more immune depressed patients who started lopinavir/r achieved >200 T cells/μL at week 48 with respect to those from the efavirenz group (not statistically significant).

In confirmation of previous data on the emergence of resistance, only the patient who presented a virological failure during the efavirenz-based regimen showed mutations that conferred resistance to efavirenz, while no drug-resistance mutations to protease inhibitors appeared in the patient whose lopinavir/r regimen failed. These data, which were also observed in ACTG 5142 (Riddler et al., 2008), highlight the high genetic barrier of ritonavir-boosted PIs and their preserved antiviral efficacy after a virological failure.



Group	Baseline	12 Weeks	24 Weeks	36 Weeks	48 Weeks
EFV	193 (±122)	333(±214)	319 (±210)	326 (±232)	491 (±244)
LPV/r	191(±127)	332(±208)	361 (±218)	381(±238)	440 (±240)

EFV, efavirenz; LPV, lopinavir.

Fig. 3. Mean CD4 cells/μL throughout the study in both groups.

In these cases, adherence should be improved before treatment changes are recommended.

One-third of the participants discontinued treatment for different reasons, although, less than 12% of these discontinuations were related to toxicities. A slightly higher number of patients in the lopinavir/r group early interrupted the study. More participants from the efavirenz-treated group, however, stopped therapy due to toxicity; most of these cases were attributed to hypersensitivity reactions. The higher incidence of hypersensitivity reaction in subjects receiving the efavirenz-containing combination was the only unexpected result with respect to toxicity, although this finding has been suggested elsewhere. This could be explained because both abacavir and efavirenz can induce hypersensitivity. Around 5% of cases who started abacavir before the current availability of the genetic test (HLA-B*5701) presented a potentially life-threatening hypersensitivity syndrome (Phillips et al., 2005). Genetic factors influencing the immune response to some drugs, such as abacavir or NNRTIs, might confer susceptibility. Within an entire abacavir exposed cohort, the presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 had a positive predictive value for hypersensitivity of 100%, and a negative predictive value of 97%. Therefore, the determination of HLA-B*5701 before starting abacavir has significantly reduced the incidence of hypersensitivity reactions and the rate of therapy discontinuations for this reason (Mallal et al., 2002, 2008). The results of our trial would have been much better if the genetic test had been available at that time, and there would have been fewer hypersensitivity-related discontinuations, mainly in the efavirenz group.

No unexpected data on lipid profile were found in the study. A more favourable lipid profile was observed in patients receiving efavirenz than in those receiving lopinavir/r due to the higher HDL-cholesterol levels achieved. In general, NNRTI-based combinations are associated with a more favourable lipid profile than PI-based therapies. Data on the benefit of efavirenz for HDL-cholesterol have already been published by our and other groups (Negredo et al., 2004).

No objective data on changes in body fat distribution were collected during the study; however, at least after 48 weeks of follow-up, only one patient had reported any changes with any regimen.

In conclusion, in spite of the limited sample size and short follow-up, this is the first randomized trial to compare both recommended antiretroviral regimens as first-line choices for the treatment of chronically HIV-infected patients using the same nucleoside backbone in both groups, Kivexa®. This exploratory analysis suggests similar virological effectiveness for efavirenz and lopinavir/r at 48 weeks, while slightly better immunological improvement was observed with efavirenz. The higher rate of discontinuations due to adverse events in the efavirenz group was mainly attributed to a higher incidence of hypersensitivity reaction related to the simultaneous use of abacavir and efavirenz. The use of the new formulation of lopinavir/r and the HLA-B*5701 genotype test before starting abacavir should improve the safety profile of these regimens.

Conflict of interest

None of the authors has a financial or beneficial interest in the products or concepts mentioned in the present article or in competing products that might bias his or her judgment. None of them is in association with any organization that could pose a conflict of interest on the points described on the manuscript.

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