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Monotherapy with Lopinavir/Ritonavir as Maintenance After HIV-1 Viral Suppression: Results of a 96-Week Randomized, Controlled, Open-Label, Pilot Trial (KalMo Study)

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Background: Long-term adverse events and expenses associated with HAART have led to an interest in simplified therapy. Lopinavir/ritonavir monotherapy is attractive due to its potency and high genetic barrier. **Methods:** This is a 96-week, open-label, randomized study to assess the feasibility of using LPV/r monotherapy in patients with undetectable viral load after being on successful HAART for at least 6 months. Subjects were randomized (1:1) to either switch from HAART to LPV/r monotherapy or to maintain their previous regimen. **Results:** 60 patients were enrolled. Baseline characteristics were similar in both groups. At Week 96, by intention-to-treat analysis, 24/30 (80.0%) subjects in monotherapy group and 26/30 (86.6%) in the control group had a plasma viral load of <80 copies/mL. There was one virologic failure (defined as VL > 500 copies/mL) in each arm. Genotyping testing identified no resistance-associated mutations. The patient on the monotherapy arm was successfully resuppressed to <80 copies/mL after intensification with tenofovir and lamivudine. No statistically significant differences were found with regard to changes in CD4 counts. One subject in the monotherapy group discontinued due to diarrhea. Five subjects in the control group underwent regimen changes due to drug-related toxicities. Viral load from semen samples collected at the end of follow-up was undetectable on 14/15 patients randomized to monotherapy. **Conclusions:** Switching from various HAART regimens to LPV/r monotherapy in patients who were virologically suppressed and without a history of previous virologic failure was effective, safe, and well tolerated through 96 weeks. **Key words:** *HIV, lopinavir/ritonavir, maintenance, monotherapy*

Boosted protease inhibitor (PI) regimen simplification has been assessed both as initial therapy[1] and as part of an induction-maintenance strategy in which patients with virologic suppression who are receiving combination therapy switch regimens to a boosted PI alone.[2, 3] Monotherapy as a maintenance strategy after successful viral suppression is attractive for sparing other classes of drugs, ease of administration, reduced toxicity compared to three-drug therapy, and drug cost reduction. Ritonavir-boosted lopinavir (lopinavir/r), for its tolerability and high genetic barrier to resistance, is a suitable candidate for maintenance monotherapy, a strategy supported by results from pilot studies[2, 4] and one randomized clinical trial (the OK04 study).[3] The OK04 study compared maintenance with lopinavir/r monotherapy with continuing lopinavir/r and two nucleoside analogue reverse transcriptase inhibitors (NRTIs) in patients with suppressed HIV plasma viral load (PVL) and found no significant difference in virological rebound after 96 weeks. The fact that the study included only patients receiving two NRTIs and lopinavir/r prior to

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inclusion does not allow generalizing its conclusions to other regimens.

We report the 96-week results of an open-label, randomized, exploratory clinical trial assessing the efficacy of switching to a lopinavir/r monotherapy versus maintaining triple-drug regimen in patients who had successful virological suppression without prior virologic failure.

METHODS

Study Design

This open-label, randomized clinical trial was conducted in two clinics in Rio de Janeiro, Brazil. Patients were included if they were HIV-1 infected, aged 18 or older, had evidence of virologic suppression at levels below 80 copies/mm^3 (lower limit of Nucleic Acid Sequence Based Amplification [NASBA] assay, most widely available at that time in Brazil), on a stable HAART regimen for at least 6 months, CD4 levels >200 cells/mm^3 at screening, and CD4 nadir > 100 cells/mm^3. Pregnant or breastfeeding women and patients who had a previous history of an AIDS-defining condition, virologic failure, or intolerance to lopinavir were not included. A written informed consent was obtained from all patients, and the study was approved by the institutional review boards of the participating sites (ClinicalTrials.gov reference NCT00160849).

Randomization and Intervention

Patients were centrally randomized 1:1 to maintain their current HAART regimen (control arm) or to switch to lopinavir/r monotherapy 400 + 100 mg bid (monotherapy arm). Participants randomized to the monotherapy arm who were on a nonnucleoside (NNRTI)-based regimen at screening were prescribed 533 + 133 mg bid of lopinavir/r for the first 2 weeks because of the possible pharmacokinetic interaction and the long half-life of the NNRTIs. Clinical assessment, adherence, and laboratory parameters were recorded at baseline and at Weeks 2, 4, and 12, and then every 12 weeks until Week 96. Switches to other drugs within the same class due to toxicity in the control group were allowed. Non-boosted PI regimens could not be intensified with ritonavir during the study and boosted PI regimens could not be switched to nonboosted PI combinations.

HIV-1 RNA PVL was determined using the NASBA assay with limits of quantification of 80 copies/mL. Genotypic resistance tests were performed on samples of those with confirmed virological failure (VF) by sequencing the PR and RT genes using the ViroSeq HIV-1 genotyping system (Abbott Molecular, Des Plaines, Illinois, USA). At each study visit, plasma samples collected just before the morning dose were stored at –70°C for determination of lopinavir levels in patients with loss of virologic suppression. Plasma concentration of lopinavir was determined with a high-performance liquid chromatographic assay. Adherence was assessed by both pill count at each visit and an adherence questionnaire assessing the last 3 days' doses.[5]

Semen samples from male volunteers randomized to monotherapy arm were collected on their last visit to determine viral load on seminal plasma by real-time polymerase chain reaction (PCR).

Safety Analysis

All patients who received at least one dose of the study medications were included in the primary safety analysis at 96 weeks. Safety assessment included medical histories, physical examinations, laboratory evaluations, and reports of adverse events. Toxicities were graded according to ACTG toxicity grading table (2004).

Definitions and Endpoints

VF was defined as two consecutive measures of HIV-1 PVL >500 copies/mL within an interval of 4 (±1) weeks. The primary endpoint of the study was the proportion of patients with PVL <80 copies/mL of HIV RNA at Week 96 on intention-to-treat (ITT) analysis with all missing data counting as failure. The secondary endpoints were to assess the following: incidence of AIDS-defining illnesses; CD4 cells count changes during the study period; and incidence of antiretroviral-related clinical and laboratory adverse events including changes in anthropometric measures and lipids profile.

Statistical Analysis

Proportions between the two arms were compared by chi-square or Fisher exact test when appropriate and continuous variables were compared by

t test of Wilcoxon rank sum test. Marginal models using the generalized estimating equations (GEE) approach and assuming unstructured correlation matrix to account for intra-individual correlation were fitted to assess changes in CD4 cell counts, laboratory, and metabolic parameters. Kaplan-Meier survival curves were constructed to describe time to failure, and the log rank test was used to compare time to failure between the two arms. All statistical analyses were performed with Stata version 9.0 (Stata Corp., College Station, Texas, USA). All reported *p* values are two sided.

This study was partially supported by Abbott Laboratories. The protocol was originally designed by the first author. All the authors contributed to the final version of the protocol and had independent access to the outcome and safety data. The analyses were done using the data collected and kept centrally at the Praça Onze site.

RESULTS

Baseline Characteristics

From August 2004 to February 2005, 60 subjects were randomized to lopinavir/r monotherapy ($n=30$) or to maintain their current regimen ($n=30$). Baseline characteristics are demonstrated on **Table 1,** and disposition of the patients are shown in **Figure 1**. The two groups were comparable with regard to age, gender, CD4 count, and mean time on HAART. NNRTI-based regimens consist of efavirenz in most of the cases and the PIs used were nelfinavir or indinavir/r, with only one patient on a lopinavir/r-based regimen.

Efficacy

At Week 96, by ITT analysis, 26/30 (86.7%; 95% CI, 74.5–98.8) and 24/30 (80.0%; 95% CI, 65.7–94.3) subjects in the control and monotherapy arms remained virologically suppressed ($p=.48$). On-treatment analysis including only patients who completed 96 weeks of follow-up without discontinuation for reasons other than VF showed 96% efficacy in both groups (24/25 patients in the monotherapy group and 26/27 patients in the control group).

At Week 96, no statistically significant differences in median CD4 count changes were observed between the control and the monotherapy arms (42 [IQR 35 to 133] and 91 [IQR –55 to 169], respectively; $p=.93$). No AIDS-defining conditions occurred during the study period. One case of tuberculosis in the monotherapy group was not considered to be associated with immunosuppression, because it was a localized presentation (vertebral tuberculosis); at the last visit before this diagnosis, the patient did not show a significant decrease in CD4 count or loss of virologic suppression.[6]

Table 1. Baseline characteristics of the study population

Variable	LPV/r arm ($n=30$)	Control arm ($n=30$)	*p*
Male gender	17 (54.8)	20 (69.0)	.59
Age, years	39 (31–46)	40 (31–46)	.73
CD4 cell count, cells/mm^3	538 (365–738)	510 (355–608)	.42
Race/ethnicity			
Caucasian	10 (33.3)	9 (30.0)	.55
Black	4 (13.3)	5 (16.6)	1.00
Other	16 (53.4)	16 (53.4)	1.00
Hepatitis C	3 (10)	1 (3.3)	1.00
Hepatitis B	0	0	
Prior antiretroviral therapy			
Time, months	40.5 (12–84)	43.4 (10–101)	
Protease inhibitors (PI)	10 (33.3)	9 (30.0)	1.00
Nonnucleoside inhibitors (NNRTI)	19 (63.3)	19 (63.3)	1.00
PI + NNRTI	0	2 (6.7)	.49
Three nucleoside inhibitors	1 (3.4)	0	1.00

Note: Values given are either *n* (%) or median (interquartile range).

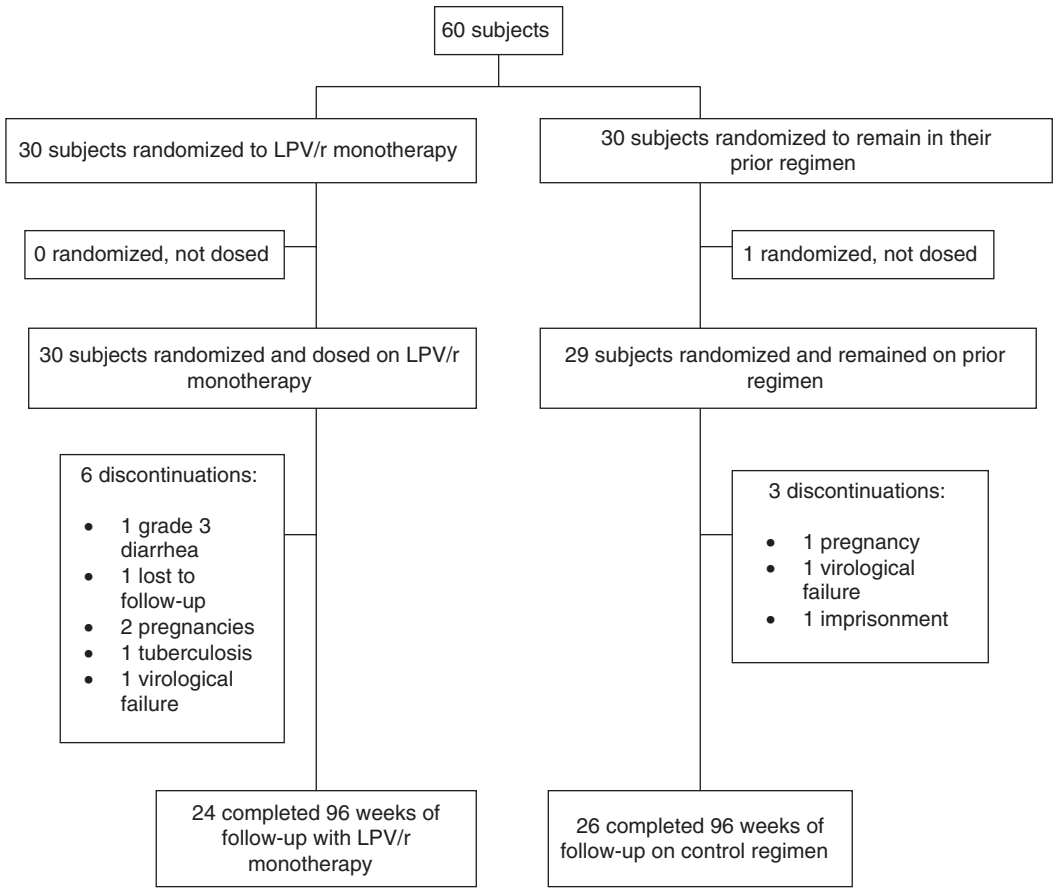

Figure 1. Subject disposition through 96 weeks.

Virologic Failure

One patient in each arm met the protocol definition for VF. The patient on monotherapy experienced VF on Week 48; a sample collected at that point showed a lopinavir plasma level of 2,984 ng/mL, slightly below therapeutic range, despite lack of adherence not having being identified (above 95% as recorded by pill count). Resistance testing identified no resistance-associated mutations. In this case, VL was successfully resuppressed to <80 copies/mL after intensification with tenofovir and lamivudine. The subject in the control arm experienced VF at Week 36; his HAART regimen was estavudine, didanosine, and nelfinavir, and no resistance-associated mutations were found upon genotyping.

Safety

Clinical adverse events observed during the study period are shown in **Table 2**. More patients in the monotherapy arm experienced gastrointestinal side effects (24 vs. 10 in monotherapy and maintenance arms, respectively; $p = .001$), including one study discontinuation due to diarrhea. No other statistically significant differences were detected between the two study arms. In the control arm, five subjects had their regimen changed due to drug-related toxicities, three patients switched from stavudine to tenofovir, one patient switched from indinavir to atazanavir, and one patient switched from didanosine to lamivudine. There were two cases of grade 3 abnormality of triglycerides, all of them in the control group. Additionally, there were three patients in the control group and two patients in the monotherapy group who presented grade 3 abnormalities of cholesterol. No other clinically significant laboratory abnormalities of grades 3 or 4 were observed in any of the study groups.

Seminal Plasma Results

Semen was collected from 15 male volunteers randomized to monotherapy arm, all of them on Week 96. Fourteen volunteers (94.1%) had

Table 2. Adverse events occurred during the study period

Event	LPV/r arm (n = 30) n (%)	Control arm (n = 30) n (%)	P
Respiratory tract	15 (50.0)	19 (63.3)	.43
Skin (including rash)	18 (60.0)	18 (60.0)	1.00
Genitourinary tract	5 (16.7)	8 (26.7)	.53
Musculoskeletal	7 (23.3)	10 (33.3)	.56
Neurological	7 (23.3)	8 (26.7)	1.00
Gastrointestinal	24 (80.0)	10 (33.3)	.001
Pain	8 (26.7)	9 (30.0)	1.00
Others	11 (36.7)	14 (46.7)	.60

VL <40 copies/mL and one had low level detectable viral load (260 copies/mL).

DISCUSSION

This was a pilot study designed to investigate the feasibility of simplification to lopinavir/r as monotherapy in long-term, virologically suppressed HIV-infected patients on HAART. Our findings indicate that this strategy successfully maintained virological suppression for 96 weeks in most patients, regardless of the background HAART regimen.

The high efficacy of lopinavir/r monotherapy in maintaining virological suppression shown in this study is comparable to that of the OK04 study, which also involved patients with at least 6 months of sustained viral suppression.[3] However, different from that study, the inclusion of various background HAART regimens, mostly NNRTI-based regimens, yields generalizability to our findings, in particular to other resource-limited settings.

In contrast to the favorable results demonstrated in controlled trials, Sprinz et al found a 37% failure rate among 27 subjects who switched to lopinavir/r monotherapy after successful virological suppression with HAART.[7] One likely explanation for such discrepant results is that, although subjects with a previous history of VF were not included in our study, nearly 60% of patients in the study of Sprinz et al had had VF before achieving successful suppression, including PI-based regimens if no primary PI mutation was detected on baseline.

Only three patients randomized to the monotherapy group presented detectable viremia at any point during the follow-up and all cases were successfully resuppressed: two while still on lopinavir/r monotherapy and one after intensification with tenofovir and lamivudine. Published data so far suggest that lopinavir/r monotherapy is rarely associated with development of significant genotypic resistance even when virological suppression is not maintained.[3,4,8] In one study, evaluating lopinavir/r monotherapy as maintenance therapy after an initial inducing phase of lopinavir/r plus AZT/3TC compared to efavirenz plus AZT/3TC, low-level viremia was more frequent in the induction-maintenance arm,[8] but most patients regained virological suppression while still on lopinavir/r monotherapy. In a systematic review of lopinavir/r monotherapy recently published, only 10 cases of PI mutations were found during the follow-up of 570 patients treated with this strategy.[9] Nevertheless, there is a concern that prolonged low-level viremia associated with boosted PI monotherapy strategy may lead to drug resistance. Due to its short terminal half-life, it can be hypothesized that a suboptimal adherence may have a more deleterious impact on virologic suppression in patients receiving lopinavir/r monotherapy than in recipients of combined therapy. Additionally, the long-term use of regimens containing drugs from multiple classes may contribute to suppressing viral replication in compartments where PIs are known to have limited penetration, such as cerebrospinal fluid and genital secretions.[10,11] It was suggested that poor penetration on virologic sanctuaries could be associated with the higher frequency of low-level viremia on first-line studies with PI/r monotherapy compared to maintenance strategies.[12] In our study, viral replication was not detected in the vast majority of seminal samples collected, suggesting VL in this compartment may still be suppressed in this population even after 96 weeks of PI monotherapy. This finding is also relevant

because suboptimal viral suppression on genital fluid could have an impact on sexual transmission.

Despite the use of the older soft gel formulation, lopinavir/r was generally well tolerated, with only one patient interrupting treatment due to a clinical adverse event (grade 2 diarrhea). In fact, gastrointestinal symptoms were the only group of side effects that was found significantly more frequently in the monotherapy arm, consistent with other trials involving lopinavir/r. [13] The low incidence of side effects in the control arm may reflect the fact that these patients had been on the same regimen for at least 6 months prior to entering the study.

The most important limitation of our study is the small sample size. Thus, the power to detect a difference in efficacy was low. However our data are consistent with the meta-analysis done in a systematic review of lopinavir/r monotherapy that found a risk of loss of virologic supression with this strategy of 22.6%.[9] There was no loss of therapeutic options during our study, because the only case of VF was successfully suppressed after reintroduction of the nucleosides. In addition, we demonstrated a strong correlation of semen VL with PVL even using monotherapy with a drug that shows poor penetration in this site. As far as we know, this is the largest series of reported data from VL on seminal plasma including patients on lopinavir/r monotherapy.

Our results have public health implications. Our findings suggest that simplification with a boosted PI monotherapy after successful virological suppression could be a feasible strategy in resource-limited settings, reducing costs and toxicity and lowering the pill burden. No new nucleoside/nucleotide analogues for HIV treatment have become available in the last 5 years, and even the newer, more expensive options in this class are still raising concerns regarding efficacy and toxicity. Although drugs from new classes such as integrase inhibitors and CCR5 antagonists recently made available may be combined with boosted PI in nucleoside-sparing regimens, the high cost of these drugs will likely limit their use in low-income countries.

In conclusion, in this exploratory trial, switching long-term suppressed patients with no history of VF from different background HAART regimens to lopinavir/r monotherapy has shown to be safe and effective. More data from larger studies in different clinical settings are needed to confirm our results, particularly in resource-limited settings where such strategy could represent a feasible alternative. The cost-effectiveness of such a strategy needs to be assessed and should take into account the widespread problem of inadequate laboratory capacity to monitor VL in these settings and the impact of low-level viremia, more frequently associated with this strategy.

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REFERENCES

1. Delfraissy JF, Flandre P, Delaugerre C, et al. MONARK trial (MONotherapy AntiRetroviral Kaletra): lopinavir/ritonavir (LPV/r) monotherapy or plus zidovudine and lamivudine in antiretroviral-naive HIV infected patients. *AIDS.* 2008;22:385–393.
2. Campo RE, Lalanne R, Tanner TJ, et al. Lopinavir/ritonavir maintenance monotherapy after successful viral suppression with standard highly active antiretroviral therapy in HIV-1-infected patients. *AIDS.* 2005;19:447–449.
3. Arribas JR, Delgado R, Arranz A, et al. Lopinavir-ritonavir monotherapy versus lopinavir-ritonavir and two nucleosides for maintenance therapy of HIV: 96-week results. *J Acquir Immune Defic Syndr.* 2009;51:142–157.
4. Arribas JR, Pulido F, Delgado R, et al. Lopinavir/ritonavir as single-drug therapy for maintenance of HIV-1 viral suppression: 48-week results of a randomized, controlled, open-label, proof-of-concept pilot clinical trial (OK Study). *J Acquir Immune Defic Syndr.* 2005;40:280–287.
5. Chesney MA, Ickovics JR, Chambers DB, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. Patient Care Committee & Adherence Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). *AIDS Care.* 2000;12:255–266.
6. Badri M, Ehrlich R, Pulerwitz T, et al. Tuberculosis should not be considered an AIDS-defining illness in areas with a high tuberculosis prevalence. *Int J Tuberc Lung Dis.* 2002;6(3):231–237.

7. Sprinz E, Bay MB, Lazzaretti RK, et al. Lopinavir/ritonavir monotherapy as maintenance treatment in HIV-infected individuals with virological suppression: results from a pilot study in Brazil. *HIV Med.* 2008;9:270–276.
8. Cameron W, da Silva BA, Arribas J, et al. A 96-week comparison of lopinavir-ritonavir combination therapy followed by lopinavir-ritonavir monotherapy versus efavirenz combination therapy. *J Infect Dis.* 2008;198:234–240.
9. Bierman WF, van Agtmael MA, Nijhuis M, Danner SA, Boucher CA. HIV monotherapy with ritonavir-boosted protease inhibitors: a systematic review. *AIDS.* 2009; 23(3):279–291.
10 Vergara TR, Estrela RC, Suarez-Kurtz G, et al. Limited penetration of lopinavir and ritonavir in the genital tract of men infected with HIV-1 in Brazil. *Ther Drug Monitor.* 2006;28:175–179.
11. Vernazza P, Daneel S, Schiffer V, et al. The role of compartment penetration in PI-monotherapy: the Atazanavir-Ritonavir Monomaintenance (ATARITMO) Trial. *AIDS.* 2007;21:1309–1315.
12. Sahali S, Chaix M, Delfraissy JF, et al. Ritonavir-boosted protase inhibitor monotherapy for the treatment of HIV-1 infection. *AIDS Rev.* 2008;10: 4–14.
13. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lancet.* 2008;372(9639): 646–655.

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