

## A 96-Week Comparison of Lopinavir-Ritonavir Combination Therapy Followed by Lopinavir-Ritonavir Monotherapy versus Efavirenz Combination Therapy

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**Antiretroviral-naïve HIV-1-infected volunteers received zidovudine/lamivudine plus either lopinavir/ritonavir ( $n = 104$ ) or efavirenz ( $n = 51$ ). Lopinavir/ritonavir-treated subjects demonstrating 3 consecutive monthly HIV-1 RNA levels  $<50$  copies/mL started lopinavir/ritonavir monotherapy. In previous-failure=failure analysis, 48% (lopinavir/ritonavir) and 61% (efavirenz) maintained HIV-1 RNA at  $<50$  copies/mL through week 96, ( $P = .17$ ; 95% confidence interval [CI] for the difference,  $-29\%$  to  $4\%$ ); in noncompletion=failure analysis, 60% (lopinavir/ritonavir) and 63% (efavirenz) maintained HIV-1 RNA at  $<50$  copies/mL at week 96 ( $P = .73$ ; 95% CI for the difference,  $-19\%$  to  $13\%$ ). Significant sparing of peripheral lipotrophy was noted in the lopinavir/ritonavir simplification strategy. This study has provided important information for future studies using treatment simplified to lopinavir/ritonavir monotherapy.**

**Trial registration.** ClinicalTrials.gov identifier: NCT00075231.

Several reports have suggested that lopinavir/ritonavir monotherapy may be an effective therapeutic option for treatment of HIV-1 infection in antiretroviral-naïve patients [1–8]. Recently, the OK04 study demonstrated that subjects who experienced

virologic suppression while receiving lopinavir/ritonavir and 2 nucleoside reverse-transcriptase inhibitors (NRTIs) and whose treatment then was simplified to lopinavir/ritonavir monotherapy maintained virologic suppression at rates similar to those in subjects who continued the triple combination therapy (85% vs. 90%, respectively, for the proportion of subjects maintaining HIV-1 RNA at  $<50$  copies/mL;  $P = .31$ ) through 48 weeks [9]. In contrast, the MONARK trial showed that, at week 48, the frequency of HIV-1 RNA at  $<50$  copies/mL was lower in subjects initiating antiretroviral therapy with lopinavir/ritonavir monotherapy than in subjects initiating antiretroviral therapy with lopinavir/ritonavir plus NRTIs (84% vs. 98%, respectively;  $P = .03$ ) [10].

The present study compares, in antiretroviral-naïve subjects who were monitored through 96 weeks, a strategy of treatment with lopinavir/ritonavir plus lamivudine/zidovudine followed by lopinavir/ritonavir monotherapy versus a standard regimen of efavirenz plus lamivudine/zidovudine.

**Subjects, materials, and methods.** A total of 155 antiretroviral-naïve subjects with plasma HIV-1 RNA at  $>1000$  copies/mL, any CD4<sup>+</sup> T cell count, and absence of resistance to the drugs used in the present study were randomized 2:1 to receive either open-label lopinavir/ritonavir (dose, 400 mg/100 mg in a soft-gelatin capsule) twice daily or efavirenz (dose, 600 mg) once daily; all subjects received coformulated lamivudine/zidovudine (dose, 150 mg/300 mg) twice daily. Between weeks 24 and 48, subjects treated with lopinavir/ritonavir whose plasma HIV-1 RNA was at  $<50$  copies/mL at 3 consecutive measurements discontinued treatment with lamivudine/zidovu-

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dine. For subjects receiving lopinavir/ritonavir monotherapy who experienced confirmed virologic rebound of HIV-1 RNA to >500 copies/mL at 2 consecutive measurements 1 month apart, reintensified therapy with NRTIs was initiated; for subjects with confirmed HIV-1 RNA values of 50–500 copies/mL, such reintensified therapy was permitted but was not required. The study was approved by either the institutional review board or the ethics committee at each center, and all enrolled subjects provided written informed consent.

Subjects were assessed every 4 weeks through week 72, then every 8 weeks through week 96. Dual x-ray absorptiometry (DEXA) scans assessed by a single evaluator were performed at baseline and every 24 weeks thereafter. Two-hour oral glucose (75 g)–tolerance tests (OGTT) were performed at baseline and at weeks 24 and 96. Resistance genotyping was performed during screening (TRUGENE HIV-1; Bayer Health Care). An independent data-monitoring committee assessed the data every 3 months.

Samples from subjects without HIV-1 RNA at <500 copies/mL by week 24 or with confirmed virologic rebound to >500 copies/mL were submitted for drug-resistance testing. Resistance to lopinavir was defined as (1) the emergence of any protease mutation leading to an amino acid substitution at locus 8, 30, 32, 46, 47, 48, 50, 54, 82, 84, or 90 or (2) the emergence of 3 or more mutations, not present at screening, at locus 10, 20, 24, 36, 53, 63, or 71.

The planned sample size of 150 subjects provided 80% power to detect a 25% difference in the week-96 response rate, as well as 70% power to detect a 20% difference in the mean change in limb-fat percentage through 96 weeks, on the basis of a common SD of 40%.

Two populations were considered for analysis: (1) an intent-to-treat exposed (ITT-E) population, which included all subjects receiving at least 1 dose of study medication, and (2) a “simplified-treatment” population, which included subjects who received lopinavir/ritonavir monotherapy. The primary efficacy end point was the proportion of subjects, in the ITT-E population, with HIV-1 RNA at <50 copies/mL at week 96 when a previous-failure=failure analysis was used: responders were defined as those with plasma HIV-1 RNA at <50 copies/mL at week 96 who had not previously experienced confirmed virologic rebound (to >50 copies/mL); nonresponders were defined as those who either did not complete 96 weeks of treatment, had HIV-1 RNA at >50 copies/mL at week 96, or experienced confirmed virologic rebound before week 96. A secondary analysis used noncompletion=failure methodology, in which responders had HIV-1 RNA at <50 copies/mL at week 96, regardless of prior confirmed virologic rebound or reintensified therapy with NRTIs. Differences between the treatment groups were compared by use of Fisher’s exact test. In the simplified-treatment population, Kaplan-Meier estimates of the time to loss of virologic response, from initiation of lopinavir/ritonavir monother-

apy through week 96, were calculated and compared with a subset of efavirenz-treated subjects with HIV-1 RNA at <50 copies/mL at 3 consecutive measurements.

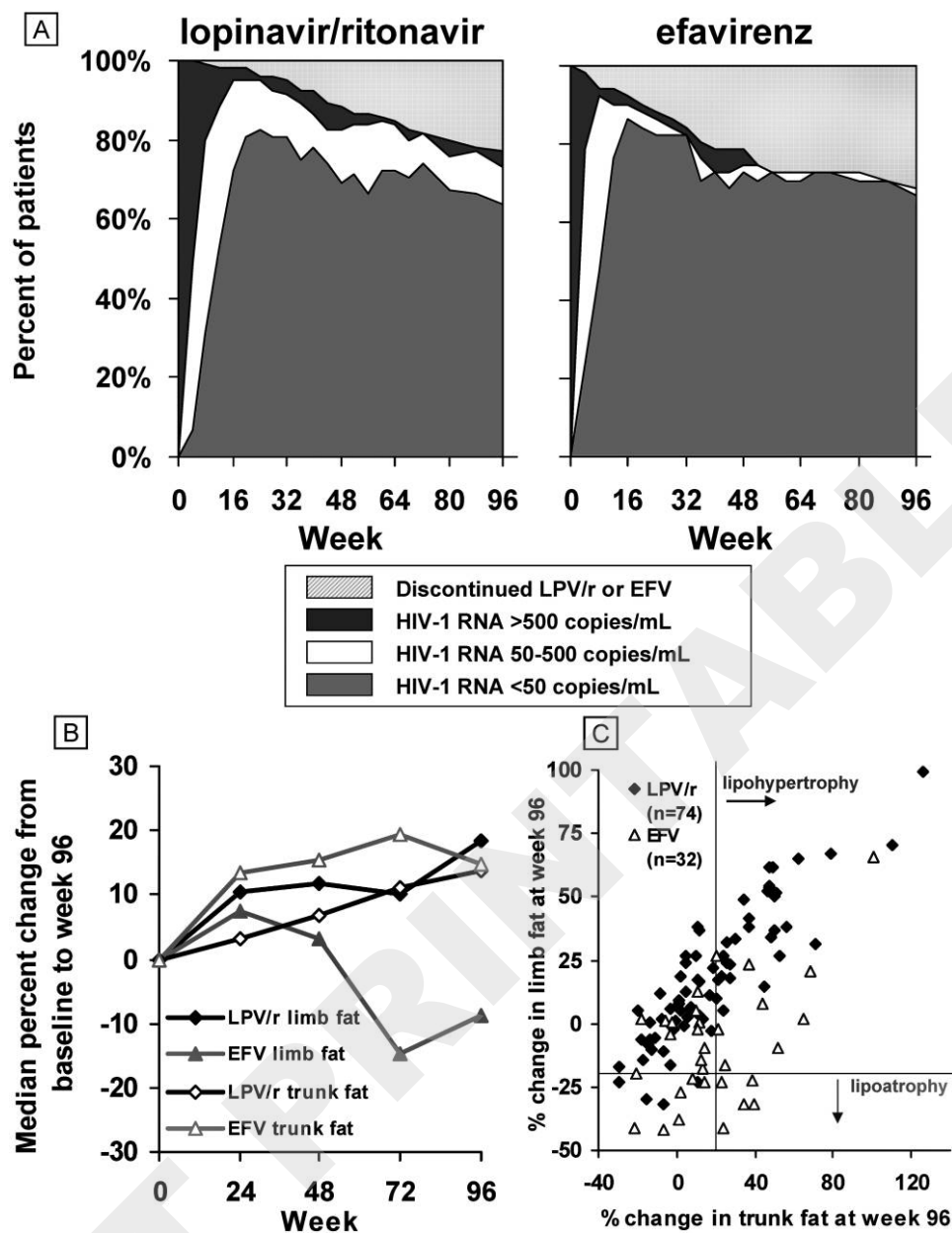
The groups were compared in terms of changes (from baseline to week 96) in laboratory-measured parameters, homeostasis model assessment (HOMA) [11], and DEXA scans, by use of analysis of variance among the subjects who completed 96 weeks of treatment.

Lipoatrophy (defined as >20% loss in limb fat) and lipohypertrophy (defined as >20% gain in trunk fat) were compared between the groups by use of Fisher’s exact test. Impaired glucose tolerance (IGT) (2-h glucose at 140–199 mg/dL) and diabetes mellitus (DM) (2-h glucose at >200 mg/dL) were assessed at baseline and at week 96.

**Results.** A total of 156 subjects were randomized, including 1 who did not receive the drugs used in the study. The remaining 155 subjects (104 of whom received lopinavir/ritonavir and 51 of whom received efavirenz) were enrolled. Subjects were generally male (79%) and white (65%), with a mean age of 38 years and a mean baseline HIV-1 RNA level of 4.9 log<sub>10</sub> copies/mL. Baseline characteristics of the groups were similar, except that subjects in the lopinavir/ritonavir treatment group had a higher mean baseline HIV-1 RNA and a higher mean age; sensitivity analyses controlling for baseline HIV-1 RNA and age indicated that these 2 variables did not meaningfully affect the overall results of the study (data not shown). Overall, 112 subjects (71%, comprising 75% of those treated with lopinavir/ritonavir and 69% of those treated with efavirenz) completed their assigned randomized treatment regimen. After a median of 24 weeks of lopinavir/ritonavir combination therapy, the treatment of 92 subjects (88%) was simplified to lopinavir/ritonavir monotherapy.

In the ITT-E population, when the previous-failure=failure end point was used, 48% of those who had received lopinavir/ritonavir combination therapy and 61% of those who had received efavirenz combination had HIV-1 RNA <50 copies/mL at week 96 ( $P = .17$ ; 95% CI for the difference, –29% to 4%). Through week 24—that is, during the period when both groups were receiving combination antiretroviral therapy—83% of the lopinavir/ritonavir treatment group and 80% of the efavirenz treatment group had HIV-1 RNA viral loads <50 copies/mL when the previous-failure=failure end point was used. In the noncompletion=failure analysis, in which both confirmed virologic rebound before week 96 and reintensified therapy with NRTIs were ignored, 60% of the lopinavir/ritonavir treatment group and 63% of the efavirenz treatment group had HIV-1 RNA at <50 copies/mL at week 96 ( $P = .73$ ; 95% CI for the difference, –19% to 13%); when a threshold of 500 copies/mL at week 96 was used, the corresponding values were 69% and 65% ( $P = .59$ ) (figure 1A).

Through the 72 weeks after treatment was simplified to lopinavir/ritonavir monotherapy, Kaplan-Meier estimates of the percentage of subjects maintaining HIV-1 RNA at <50 cop-



**Figure 1.** A, Summary of HIV-1 RNA level and discontinuation status, stratified by visit, for the subjects receiving lopinavir/ritonavir and the subjects receiving efavirenz. B, Median percent change, from baseline value, in limb fat and trunk fat, based on subjects who completed the study. C, Scatter plot of percent change, from baseline to week 96, in limb fat vs. trunk fat, for individual subjects. LPV/r, lopinavir/ritonavir; EFV, efavirenz.

ies/mL were 57% for the lopinavir/ritonavir treatment group ( $n = 88$ ) and 91% for the efavirenz treatment group ( $n = 44$ ) ( $P < .001$ , by log-rank test); when a threshold of 500 copies/mL at week 96 was used, the corresponding values were 86% and 95% ( $P = .133$ ).

Of the subjects receiving lopinavir/ritonavir monotherapy, 12 had confirmed virologic rebound to HIV-1 RNA at  $>500$  copies/mL (of the 7 subjects for whom subsequent data were available, 5 [71%] later had HIV-1 RNA at  $<50$  copies/mL—4 after NRTI intensification and 1 while still receiving lopinavir/ritonavir monotherapy), and 20 had confirmed virologic rebound to

50–500 copies/mL (of 14 subjects for whom subsequent data were available, 11 [79%] later had at least 1 measurement of HIV-1 RNA at  $<50$  copies/mL without resumption of treatment with NRTIs, and 9 of these 11 subjects completed the 96 weeks of treatment, and 7 of those 9 had HIV-1 RNA at  $<50$  copies/mL at completion of the study).

Of the subjects who completed the 96 weeks of treatment, the mean change, from baseline CD4<sup>+</sup> T cell count to week-96 CD4<sup>+</sup> T cell count was 289 cells/mm<sup>3</sup> in the lopinavir/ritonavir treatment group and 240 cells/mm<sup>3</sup> in the efavirenz treatment group ( $P = .12$ ).

Of the 16 subjects who were tested for drug resistance, 4 subjects in the lopinavir/ritonavir treatment group (3 of whom were receiving lopinavir/ritonavir monotherapy and 1 of whom was receiving triple therapy) developed protease inhibitor (PI)-resistance mutations that had not been present at screening, and 1 subject in the efavirenz treatment group had mutation K103N in reverse transcriptase (RT). In 1 subject receiving lopinavir/ritonavir monotherapy, HIV-1 RNA rebounded to >500 copies/mL at week 40; this subject's genotype showed mutations K219Q and K103N in RT and M46L and V82A in protease. Both the genotype at screening and retrospectively performed baseline genotyping showed mutation K219Q, suggesting possible infection with a drug-resistant strain of HIV-1. In another subject receiving lopinavir/ritonavir monotherapy, HIV-1 RNA rebounded to >500 copies/mL at week 44; this subject's genotype showed mutations M41L, D67N, V118I, L210W, T215Y, and Y188L in RT and L90M in protease. Although the genotype at screening showed no significant drug-resistance mutations, retrospectively performed baseline genotyping showed mutations Y181C, L210W, T215Y, and K219N in protease, suggesting infection with a drug-resistant strain of HIV-1. A third subject receiving lopinavir/ritonavir monotherapy had persistent viremia (50–500 copies/mL) beginning at week 36; genotyping showed mutation M46I in protease, a mutation that was not present at screening. One subject receiving lopinavir/ritonavir triple therapy had, at week 40, mutation M184V in RT and mutation I54V in protease.

The most common (frequency, >5%) moderate or severe adverse events related to treatment were diarrhea (15%) and nausea (14%), in the subjects receiving lopinavir/ritonavir monotherapy, and asthenia (12%), dizziness (12%), insomnia (12%), rash (10%), and depression (6%), in the subjects receiving efavirenz. Because of adverse events, 3 subjects did not complete the study, and 3 subjects died of causes unrelated to the study treatment (1 subject receiving lopinavir/ritonavir monotherapy died after ingesting ethylene glycol, 1 subject receiving lopinavir/ritonavir monotherapy died of Burkitt lymphoma, and 1 subject receiving efavirenz died of cardiac arrest). The most common (frequency, >5%) grade 3+ laboratory-detected abnormalities were total cholesterol at >7.8 mmol/L (13%), triglycerides at >8.5 mmol/L (7%), and amylase at >2 times normal upper limit (6%), in the subjects receiving lopinavir/ritonavir monotherapy, and amylase at >5 times the (10%) and alanine aminotransferase at >5 times the normal upper limit (6%), in the subjects receiving efavirenz.

Baseline and week-96 DEXA scans were available for 74 (71%) of the 104 subjects receiving lopinavir/ritonavir monotherapy and for 32 (63%) of the 51 subjects receiving efavirenz. The mean limb-fat changes, from baseline values, in the 2 groups were statistically significantly different ( $P < .001$ ), at  $\sim 2.3$  kg (figure 1B). The mean trunk-fat increases, from baseline to week 96, in the 2 groups were not significantly different, at 1.1 kg. At

week 96, the proportion of subjects with lipodystrophy was significantly less in the lopinavir/ritonavir treatment group than in the efavirenz treatment group (5% vs. 34%, respectively;  $P < .001$ ) (figure 1C), whereas the proportion of subjects with lipohypertrophy did not differ between the 2 treatment groups (45% vs. 44%, respectively;  $P > .99$ ).

Mean changes, from baseline to week 96, in 2-h OGTT and insulin did not differ either within or between the 2 treatment groups, and no significant change was observed in HOMA or in the prevalence of either IGT or DM (table 1). Statistically significant mean increases, from baseline to week 96, in lipid values were noted in both treatment groups (table 1).

**Discussion.** The present study compared treatment with lopinavir/ritonavir plus zidovudine/lamivudine, which subsequently was simplified to lopinavir/ritonavir monotherapy, versus treatment with efavirenz plus zidovudine/lamivudine, and it found that, when a standard ITT, noncompletion= failure analysis was used, the 2 treatment groups had similar proportions of subjects with suppressed HIV-1 RNA loads at week 96. It is important to note, however, that the time to confirmed virologic rebound—that is, HIV-1 RNA at >50 copies/mL—was significantly shorter in subjects receiving lopinavir/ritonavir monotherapy than for subjects receiving efavirenz. In the present study, in which subjects had suppressed HIV-1 RNA load for  $\sim 3$  months before treatment was simplified to lopinavir/ritonavir monotherapy, the rate of virologic suppression by lopinavir/ritonavir monotherapy was lower than that observed in the OK04 study, in which subjects had virologic suppression for a median of 28 months before simplified treatment [9]. Combined, the results of these 2 studies suggest that longer periods of viral suppression by combination antiretroviral therapy before treatment is simplified to lopinavir/ritonavir monotherapy may lead to better efficacy for the monotherapy regimen; data from the MONARK study also support this conclusion [10].

Virologic failures in lopinavir/ritonavir monotherapy generally occurred with low-level viremia (HIV-1 RNA at 50–500 copies/mL). Despite the low-level viremia observed in some subjects receiving lopinavir/ritonavir monotherapy, increases in CD4<sup>+</sup> T cell counts were similar in the 2 treatment groups. Virologic failure was rarely associated with the emergence of new PI-resistance mutations. It is noteworthy that, although genotype screening did not identify mutations resistant to randomized therapy in any of the subjects, in 2 of the 4 subjects who did experience new-onset PI-resistance mutations while receiving treatment, retrospective review of baseline genotypes revealed the presence of multiclass mutations. This observation suggests that the subjects had been infected with resistant virus before the study started. Detection of any drug-selected mutations at baseline may be indicative of the presence of other drug-selected mutations (including PI-resistance mutations) that are undetectable by population-level genotyping. Thus, the use of ritonavir-boosted PI monotherapy in patients with any drug-

**Table 1. Metabolic parameters: changes from baseline values.**

Variable	Lopinavir/ritonavir		Efavirenz		P <sup>a</sup>
	Subjects, no.	Value	Subjects, no.	Value	
Glucose AUC (mmol/L <sup>b</sup> × 120 min)	66		34		.52
Baseline, mean		757.7		805.3	
Change from baseline to week 96, mean ± SE		+29.4 ± 21.1	34	+5.8 ± 29.5	
Insulin AUC (mIU/mL <sup>b</sup> × 120 min)	65		31		
Baseline, mean		5594		6334	
Change from baseline to week 96, mean ± SE		-163 ± 387		-903 ± 561	.28
2-h glucose	66		34		
Baseline					.18
Missing		5 (8%)		3 (9%)	
Normal		57 (86%)		25 (74%)	
IGT		4 (6%)		6 (18%)	
DM		0 (0%)		0 (0%)	
Week 96					>.99
Missing		0 (0%)		0 (0%)	
Normal	66	63 (95%)	34	32 (94%)	
IGT		3 (5%)		2 (6%)	
DM		0 (0%)		0 (0%)	
Homeostasis model assessment	73		32		.18
Baseline, mean		2.23		2.39	
Change from baseline to week 96, mean ± SE		-0.23 ± 0.49		0.97 ± 0.74	
Cholesterol, mmol/L					
Total	76		34		.17
Baseline, mean		4.15		4.12	
Change from baseline to week 96, mean ± SE		+1.48 <sup>b</sup> ± 0.16		+1.09 <sup>b</sup> ± 0.23	
Grade 3/4 (>7.8 mmol/L) through week 96		13/104 (13%)		2/51 (4%)	
HDL	76		34		.81
Baseline, mean		1.04		1.11	
Change from baseline to week 96, mean ± SE		+0.36 <sup>b</sup> ± 0.04		+0.39 <sup>b</sup> ± 0.06	
LDL	76		33		.14
Baseline, mean		2.56		2.56	
Change from baseline to week 96, mean ± SE		0.83 <sup>b</sup> ± 0.10		0.52 <sup>b</sup> ± 0.16	
Triglycerides, mmol/L	76		33		.06
Baseline, mean		1.45		1.35	
Change from baseline to week 96, mean ± SE		+1.03 <sup>b</sup> ± 0.16		+0.49 <sup>b</sup> ± 0.24	
Grade 3/4 (>8.5 mmol/L) through week 96		7/104 (7%)		0/51 (0%)	

**NOTE.** Baseline values are pretreatment values for subjects for whom data were available at week 96. AUC, area under the curve; DM, diabetes mellitus; IGT, impaired glucose tolerance.

<sup>a</sup> For between-group comparisons of the change from baseline to week 96.

<sup>b</sup> Statistically significant ( $P < .05$ ) within-group change from baseline value.

selected resistance mutations at baseline should be undertaken with caution.

Although several short-term studies of healthy volunteers have suggested the presence of insulin resistance after short-term exposure to lopinavir/ritonavir [12, 13], the present study found, for both the lopinavir/ritonavir regimen and the efavirenz regimen, that glucose tolerance, as measured by OGTT and HOMA, did not identify an increase in insulin resistance through the 96 weeks of the study.

Last, the present study found that limb-fat loss occurred significantly less frequently in the lopinavir/ritonavir treatment

group; although this group did have less exposure to NRTIs (because its treatment was simplified to lopinavir/ritonavir monotherapy), this finding is consistent with what was observed in ACTG Study A5142: ACTG Study A5142 showed that rates of lipotrophy observed for lopinavir/ritonavir-based treatment were consistently lower than those for efavirenz-based treatment, regardless of whether treatment also included NRTIs, a finding suggesting that the differences in the occurrence of lipotrophy that were observed in the present study are attributable, at least in part, to the use of lopinavir/ritonavir rather than efavirenz [14]. Lipohypertrophy occurred with similar fre-

quency in the 2 treatment groups, suggesting that trunk-fat gain may not be related to a particular class (e.g., PI or non-NRTI) of antiretroviral drugs.

The present study has several limitations. Although it represents the largest randomized study comparing its strategies, it had relatively limited power to detect small intergroup differences in efficacy. The use of NRTIs other than zidovudine/lamivudine might have resulted in different rates of lipoatrophy [14]. Trunk-fat location was not characterized. The effects that monotherapy might have had on isolated reservoirs, such as cerebrospinal fluid, were not examined. Last, a substantial proportion of subjects did not complete the study—although it should be noted that the discontinuation rates in the 2 treatment groups were not notably different.

In summary, the present study provides important information for future investigations of the lopinavir/ritonavir simplified-treatment strategy. Both the finding of significantly less peripheral lipoatrophy for a lopinavir/ritonavir-based regimen than for an efavirenz-based regimen and the absence, in both regimens, of changes in glucose tolerance are noteworthy.

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