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Lopinavir/ritonavir monotherapy versus current treatment continuation for maintenance therapy of HIV-1 infection: the KALESOLO trial

Jean-Luc Meynard[1]*, Vincent Bouteloup[2], Roland Landman[3], Philippe Bonnard[4], Vincent Baillat[5], André Cabie[6], Sami Kolta[7], Jacques Izopet[8], Anne-Marie Taburet[9], Patrick Mercie[10], Geneviève Chene[2] and Pierre-Marie Girard[1,11] on behalf of the KALESOLO Study Group†

[1]*Service des Maladies Infectieuses, Hôpital Saint-Antoine, Faculté de Médecine Pierre et Marie Curie, Paris, France;* [2]*Inserm U897, Université Victor Segalen Bordeaux 2, ISPED, Bordeaux, France;* [3]*Institut de Médecine et d'Epidémiologie Appliquée (IMEA), Faculté Bichat Claude Bernard, Paris, France;* [4]*Service des Maladies Infectieuses, Hôpital Tenon, Faculté de Médecine Pierre et Marie Curie, Paris, France;* [5]*Service des Maladies Infectieuses, Hôpital Gui de Chauliac, Montpellier, France;* [6]*Service des Maladies Infectieuses, Hôpital Zobda Quitman, Fort de France, France;* [7]*Université Paris Descartes, Service de Rhumatologie, Hôpital Cochin, Paris, France;* [8]*Inserm U563 and Service de Virologie, Hôpital Purpan, CHU de Toulouse, France;* [9]*Service de Pharmacie, Hôpital Bicêtre, Kremlin-Bicêtre, France;* [10]*Service de Médecine Interne, Hôpital Saint-André, Université Victor Segalen Bordeaux 2, Bordeaux, France;* [11]*INSERM UMR-S707, Paris, France*

*Corresponding author. Hôpital Saint-Antoine, Service de Maladies Infectieuses et Tropicales, 184 rue du Faubourg Saint-Antoine, 75012 Paris, France. Tel: +33-1-49-28-28-66; Fax: +33-1-49-28-21-49; E-mail: jean-luc.meynard@sat.aphp.fr
†Members are listed in the Acknowledgements section.

Objectives: We evaluated a monotherapy maintenance regimen with lopinavir/ritonavir versus continuing current combined antiretroviral treatment (cART) in HIV patients with suppressed plasma HIV-1 RNA.

Patients and methods: This was an open-label, non-inferiority, multicentre trial in 23 sites in France. Adults were randomized if they had no history of virological failure while receiving a protease inhibitor, maintained HIV-1 RNA <50 copies/mL for at least 6 months and did not change cART during the last 3 months. The primary endpoint was the proportion of patients with HIV-1 RNA <50 copies/mL at Week 48 (non-inferiority margin set at −12%) with missing data and treatment modification considered as failure. The trial has been registered in ClinicalTrials.gov under the identifier NCT00140751.

Results: At Week 48, 84% (73/87) of patients in the lopinavir/ritonavir monotherapy group met the primary endpoint compared with 88% (87/99) in the cART group [difference, −4.0%, lower limit of 90% two-sided confidence interval (CI) for difference, −12.4%]. In secondary analysis with success defined as plasma HIV-1 RNA <400 copies/mL, 87% (76/87) of patients in the lopinavir/ritonavir monotherapy group were virologically suppressed compared with 88% (87/99) in the cART group (difference, −0.5%, lower limit of 90% two-sided CI for difference, −8.5%). If antiretroviral treatment intensification was taken into account, 91% (79/87) of patients in the lopinavir/ritonavir monotherapy group met the primary endpoint compared with 88% (87/99) in the cART group (difference, +2.9%, lower limit of 90% two-sided CI for difference, −4.5%). Failures of lopinavir/ritonavir monotherapy did not show acquired resistance mutations in the protease gene.

Conclusions: Lopinavir/ritonavir monotherapy did not achieve non-inferiority versus cART for maintaining plasma HIV-1 RNA <50 copies/mL. Nevertheless, the incidence of virological failure was low (mostly with HIV-1 RNA <400 copies/mL) and easily managed by treatment intensification.

Keywords: treatment simplification, protease inhibitor monotherapy, maintenance therapy, lipodystrophy

Introduction

A combination of three antiretroviral treatments is the standard regimen for HIV-1 infection.[1,2] Recommended first-line regimens combine two nucleoside reverse transcriptase inhibitors (NRTIs) with one non-nucleoside reverse transcriptase inhibitor (NNRTI) or one boosted protease inhibitor (PI). Long-term toxicity such as lipodystrophy has been evidenced with thymidine analogue

NRTIs.[3] Even the more recent NRTIs are not devoid of safety issues: cardiovascular toxicity has been noted with abacavir, and renal and bone toxicity have been associated with tenofovir disoproxil fumarate (tenofovir DF).[4,5] As HIV infection has become a chronic disease, exposure of patients to combined antiretroviral treatment (cART) will be prolonged for decades and minimizing long-term toxicity of cART is an important challenge for the future. The cost of this long-term treatment in a growing number of patients is also becoming a major issue. Most antiretroviral-naive patients initiating a first-line regimen achieve undetectable plasma HIV-1 RNA. Therefore, evaluation of new maintenance strategies that might decrease side effects and cost, and improve adherence while maintaining good virological and immunological efficacy has become a priority.

Early attempts to simplify antiretroviral regimens in patients who have achieved plasma viral suppression on a cART regimen have been unsuccessful.[6,7] Simplifying regimens in controlled patients continues to be an attractive idea, particularly with new boosted PIs such as darunavir or atazanavir.[8–11]

Due to its high potency and high genetic barrier to resistance, lopinavir/ritonavir is an appropriate candidate for single-drug therapy after viral suppression.[12,13] Previous studies showed that simplifying to lopinavir/ritonavir maintenance monotherapy in virologically suppressed patients allowed for sustained viral suppression compared with continuing a lopinavir/ritonavir-containing cART regimen.[14,15] All these trials were conducted in patients already receiving lopinavir/ritonavir. The aim of our trial was to evaluate whether switching patients well controlled by various antiretroviral combinations to lopinavir/ritonavir monotherapy was not inferior to continuing current cART.

Patients and methods

Study population

The following criteria had to be met for inclusion in the study: documented HIV-1 infection; age >18 years; no previous documented history of virological failure while receiving a PI; HIV-1 RNA <50 copies/mL for at least 6 months before inclusion; no change in antiretroviral treatment during the last 3 months; and no opportunistic infection during the last 6 months. Patients with triple NRTI regimen could be included. The main exclusion criteria were pregnancy and hepatitis B treated with lamivudine or tenofovir DF.

Study design

This randomized, open-label, non-inferiority, multicentre clinical trial was performed in 23 clinical sites in France. Through a dedicated web site, patients were centrally randomized 1:1 by a trial coordinating centre to continue their current cART or to receive lopinavir/ritonavir monotherapy (400/100 mg twice a day). The randomization was stratified on clinical centre and on ongoing treatment (i.e. lopinavir/ritonavir, PI other than lopinavir/ritonavir, NNRTI). The randomization list was built using the SAS Proc Plan procedure (five blocks of size of six per stratum).

The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee for Clinical Research of Saint-Antoine Hospital, Paris. Written informed consent was obtained from each patient. The trial has been registered in ClinicalTrials.gov under the identifier NCT00140751.

Study procedure

Clinical examination, haematological tests, biochemistry, CD4 and CD8 cell counts, and plasma HIV–1 RNA were assessed at screening/baseline and every 12 week period thereafter for 48 weeks. Blood triglycerides, total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol and glucose were measured at baseline and at Weeks 24 and 48. Clinical status, adverse events and concomitant treatments were recorded at each visit. Adverse events were graded using the clinical and biological adverse events Agence Nationale de Recherches sur le Sida et les Hépatites Virales (ANRS) scale.

Patients followed in one of the 10 clinical sites with dual-energy X-ray absorptiometry (DEXA) equipment were proposed to undergo a bone mineral density evaluation at the lumbar spine, left hip and total body, at baseline and Week 48 (Hologic® and GE-Lunar® brand systems were used). Lipodystrophy was evaluated by lean and fat mass distribution in the body as calculated during total body scans. A centralized reading of DEXA scans was performed in a central facility allowing quality assurance as well as standardized analysis. Quality control of the DEXA devices was also performed to check their stability during the study.

Adherence to treatment was assessed using the standardized questionnaire developed by the ANRS.[16]

Virological analysis

Genotypic resistance tests were performed centrally at the Laboratory of Virology of Toulouse. The HIV-1 reverse transcriptase and protease genes were amplified from HIV DNA in peripheral blood mononuclear cells (PBMCs) and from plasma HIV RNA by a first-round PCR followed by nested PCR.[17,18] For HIV DNA, 1 μg of DNA extracted from total PBMCs was amplified by PCR. PCR final products were visualized on gels and purified using the QIA quick purification HIV kit (Qiagen). The purified PCR products were sequenced using the fluorescent dideoxy-terminator method (Big Dye Terminator kit; Applied Biosystems, Perkin Elmer, Foster City, CA, USA) on an Applied Biosystems 3130 automated DNA sequencer (Applied Biosystems). The amino acids at codons associated with resistance to NRTIs, NNRTIs, and PIs were identified according to the 2008 International AIDS Society list (www.iasusa.org). Mixtures of wild-type and mutant viruses were classified as drug-resistant strains. HIV drug resistance was defined according to the 2008 HIV-1 genotypic resistance interpretation algorithm of the ANRS (www.hivfrenchresistance.org).

Statistical analysis

The primary endpoint was the proportion of patients with viral load <50 copies/mL at Week 48 without modification of antiretroviral treatment during the study. Modifications of treatment included any change except dosing adaptation or replacement by a fixed combination. With a non-inferiority margin set at −12% and a proportion of success at 90%, it was calculated that 78 subjects per treatment group would be needed to demonstrate non-inferiority of the lopinavir/ritonavir group (one-sided α 5% and power 80%).

The difference in the proportion of success (as defined by the protocol) between treatment groups was calculated and its confidence interval (CI) was estimated according to the binomial law. The hypothesis of non-inferiority of the two treatment groups was tested by comparing the lower limit of the two-sided 90% CI of the difference in proportions between groups with the margin set at −12%. Patients lost to follow-up or with no HIV-1 RNA measurement at Week 48 were considered as failures (missing=failure).

The secondary endpoints were the proportion of patients with viral load <400 copies/mL at Week 48 without modification of antiretroviral

treatment during the study, proportion of patients with viral load <50 copies/mL at Week 48 with treatment intensification not considered as failure. Success with treatment intensification allowed was defined in the lopinavir/ritonavir monotherapy group by a viral load <50 copies/mL at Week 48 even if NRTIs had been reintroduced; in the current cART group, success was defined by a viral load of <50 copies/mL at Week 48 without change of treatment. Other secondary endpoints were variation in CD4 cell count, evolution of biological parameters, evolution of DEXA scan parameters, treatment adherence, and clinical and biological safety.

A logistic regression model was used to identify factors associated with therapy failure in the lopinavir/ritonavir group (primary endpoint definition). Randomization group, age, gender, elapsed time from HIV diagnosis, history of cART, baseline haemoglobin, AIDS, plasma HIV-1 RNA, time spent with plasma HIV-1 RNA <50 copies/mL prior to inclusion and adherence during follow-up were first analysed in a univariate model. Adherence was analysed according to three definitions (see below). All variables with $P \le 0.20$ in the univariate analysis were included in the multivariate model.

Among patients included in the DEXA substudy, identification of factors associated with evolution of fat mass in the legs was performed using a linear regression model. Because of a significant interaction of gender × group of randomization and the small number of women included in this substudy, evolution of soft tissue and bone mineral density were analysed separately in men and women.

Treatment adherence was performed on allocated study treatment only. Patients were considered as non-adherent if they declared having missed at least one pill during the past 4 days or not being strictly adherent during the last 4 weeks. Items 'adherence in the last 4 days' and 'adherence in the last 4 weeks' were also analysed separately.

Except for therapeutic success, between-groups comparisons were performed using χ^2 test and or Fisher's exact test for categorical variables and the non-parametric Wilcoxon test for quantitative variables with α set at 0.05.

All analyses were performed using SAS 9.1 software (SAS Institute Inc., Cary, NC, USA).

Results

Disposition of patients and characteristics at baseline

Between December 2005 and December 2006, 186 patients were randomized: 99 in the current cART group and 87 in the lopinavir/ritonavir monotherapy group (Figure 1). Due to stratified randomization on centres and ongoing treatments (NNRTI, PI, lopinavir/ritonavir), the numbers of patients in the two treatment groups were slightly unbalanced.

Baseline characteristics were similar between the groups. The median duration since HIV-1 infection was 10 years, patients had received cART for a median of 7 years and had experienced a median of three previous antiretroviral regimens (Table 1). One-third were already receiving a lopinavir/ritonavir-containing regimen at inclusion.

All patients had plasma HIV-1 RNA of <50 copies/mL except four in the current cART group and five in the lopinavir/ritonavir monotherapy group (four values <250 copies/mL, one missing data).

Virological outcomes

At Week 48, 73/87 patients (84%) in the lopinavir/ritonavir monotherapy group were virologically suppressed to <50 copies/mL for
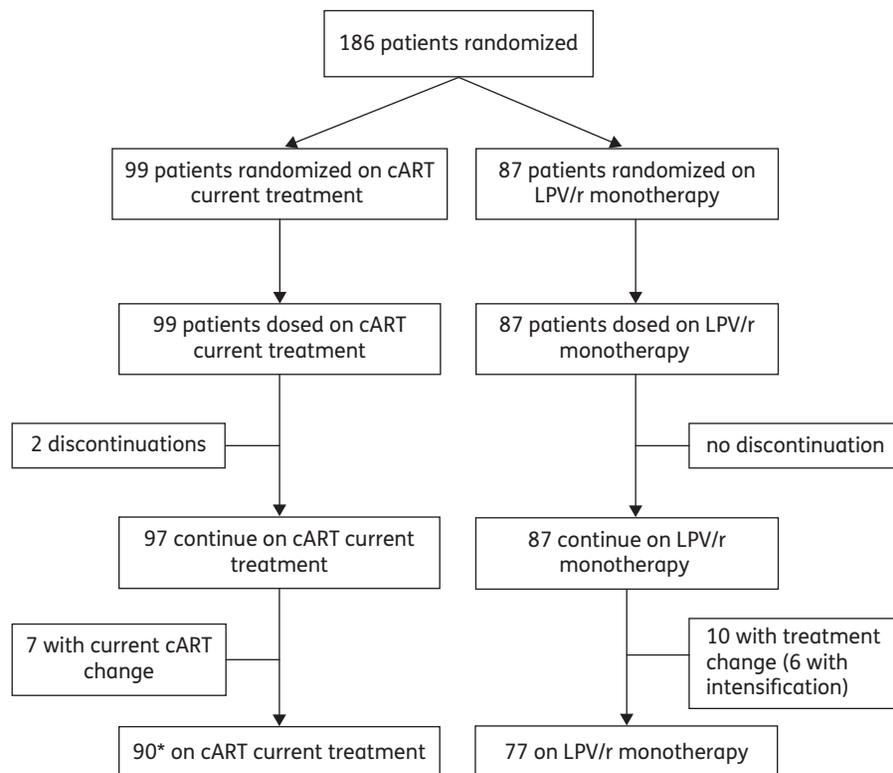

Figure 1. Patient disposition through 48 weeks, KALESOLO Study, 2005–08. LPV/r, lopinavir/ritonavir. *Visit Week 48 not done for three patients.

Table 1. Baseline characteristics in the KALESOLO Study, 2005–08

Characteristics	Current cART group (n=99)	LPV/r monotherapy group (n=87)
Male gender, n (%)	75 (76)	63 (72)
Median (IQR) age, years	43 (39–50)	44 (39–51)
CDC stage C, n (%)	27 (28)	22 (25)
HIV-1 RNA <50 copies/mL, n (%)	95 (96)	82 (94)
CD4 cell count, median (IQR), cells/mm^3	525 (357–688)	494 (371–630)
HIV infection duration, median (IQR), years	10 (5–15)	10 (4–16)
Antiretroviral treatment duration, median (IQR), years	8 (3–10)	7 (3–10)
Number of previous cART, median (IQR)	3 (2–6)	3 (2–6)
Antiretroviral treatments at inclusion, n (%)		
NRTIs		
lamivudine/emtricitabine	77 (78)	70 (80)
zidovudine	38 (38)	36 (41)
tenofovir	33 (33)	22 (25)
abacavir	21 (21)	18 (21)
didanosine	15 (15)	14 (16)
NNRTIs	25 (25)	25 (29)
PIs		
LPV/r	33 (33)	28 (32)
other PIs	41 (41)	34 (39)
Serum lipids, median (IQR), mmol/L		
triglycerides	1.48 (0.95–2.42)	1.42 (0.96–2.16)
total cholesterol	5.34 (4.87–5.88)	5.18 (4.41–5.98)
LDL-cholesterol	3.25 (2.81–3.90)	2.99 (2.38–3.91)
HDL-cholesterol	1.19 (0.98–1.50)	1.34 (1.05–1.63)
DEXA scan measurements, median (IQR), kg[a]		
truncal fat	8.2 (5.4–12.0)	8.5 (5.0–13.4)
peripheral fat (lower limbs)	4.4 (2.9–6.0)	3.6 (2.0–6.4)
Creatinine clearance[b], median (IQR), mL/min	101 (85.3–122)	104 (87.9–120)

IQR, interquartile range; LPV/r, lopinavir/ritonavir.
[a]DEXA measurements were performed in a limited number of centres (41 patients in the current cART group and 29 in the LPV/r monotherapy group).
[b]Cockcroft and Gault formula.

the primary endpoint compared with 87/99 patients (88%) in the current cART group. The percentage difference between the two groups was −4.0% with a 90% two-sided CI −12.4% to 4.5%. Non-inferiority was therefore not demonstrated on the primary outcome (Table 2).

Fourteen patients were considered as therapeutic failure in the lopinavir/ritonavir monotherapy group at Week 48. Plasma HIV-1 RNA was ≥50 copies/mL for 5 patients (62, 93, 146, 317 and 59 300 copies/mL) and 10 patients changed their regimen during the trial (one patient had both HIV-1 RNA ≥50 copies/mL and regimen change). Based on clinician's assessment, the reasons for treatment modification were: virological failure (n=8; five had added two NRTIs, one had added three NRTIs and two changed to a non-lopinavir/ritonavir-based regimen); adverse events (n=1, dyslipidaemia); and unknown in one case (viral load <50 copies/mL at time of antiretroviral treatment change). Among the five patients in the lopinavir/ritonavir arm with plasma HIV-1 RNA ≥50 copies/mL at Week 48, plasma drug concentrations were available for four patients. They were all within the therapeutic target value (8140, 7805, 5155,

5000 ng/mL). All six patients who were intensified with two NRTIs during the follow-up reached a viral load of <50 copies/mL at Week 48.

Twelve patients were considered as therapeutic failures in the current cART group: five had missing HIV-1 RNA value at Week 48, and seven changed their cART regimen (reasons: lipo-dystrophy, n=1; altered renal function, n=2; and unspecified, n=4).

The proportions of patients with viral load <400 copies/mL without treatment modification at Week 48 were 87/99 (88%) in the current cART group and 76/87 (87%) in the lopinavir/ritonavir monotherapy group (difference, −0.5%; 90% CI, −8.5% to 7.4%) (Table 2).

If antiretroviral treatment intensification was taken into account to evaluate therapeutic success at Week 48 (plasma HIV-1 RNA <50 copies/mL, addition of NRTIs allowed in lopinavir/ritonavir monotherapy group), the proportions of patients meeting the primary endpoint were 87/99 (88%) in the current cART group and 79/87 (91%) in the lopinavir/ritonavir monotherapy group (difference, 2.9; 90% CI, −4.5 to 10.4) (Table 2).

Table 2. Virological outcome at Week 48, KALESOLO Study, 2005–08

	Current cART group (*n*=99)	LPV/r monotherapy group (*n*=87)
Primary outcome (missing=failure)		
viral load <50 copies/mL without treatment change, *n* (%)	87 (88)	73 (84)
difference[a] between treatment groups (90% CI)	−4.0% (−12.4% to 4.5%)	
Reasons for failure, *n*	12	14
missing viral load	5[b]	0
HIV-1 RNA 50–400 copies/mL	0	4
HIV-1 RNA ≥400 copies/mL	0	1
antiretroviral treatment change	7	10
Secondary outcomes		
HIV-1 RNA <400 copies/mL without treatment change, *n* (%)	87 (88)	76 (87)
difference between treatment groups (90% CI)	−0.5% (−8.5% to 7.4%)	
HIV-1 RNA <50 copies/mL with intensification allowed[c], *n* (%)	87 (88)	79 (91)
difference between treatment groups (90% CI)	2.9% (−4.5% to 10.4%)	

LPV/r, lopinavir/ritonavir.
[a]LPV/r monotherapy group minus current cART group.
[b]Missing viral loads were due to premature study discontinuation (lost to follow-up, *n*=5).
[c]For analysis with treatment intensification allowed, success is defined in the LPV/r monotherapy group by a viral load <50 copies/mL at Week 48 even if NRTIs were reintroduced; in the current cART group, success is defined by a viral load <50 copies/mL at Week 48 without change of treatment.
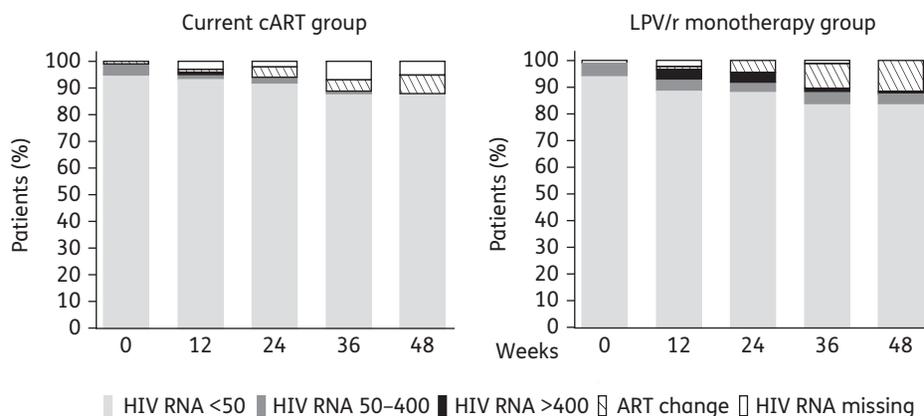

Figure 2. Point prevalence of virological response and antiretroviral treatment modification, KALESOLO Study, 2005–08. LPV/r, lopinavir/ritonavir; ART, antiretroviral treatment.

Figure 2 shows the point prevalence of antiretroviral treatment modification and virological response using 50 or 400 copies/mL HIV-1 RNA as threshold. On their allocated treatment, 8 patients in the current cART group and 18 in the lopinavir/ritonavir monotherapy group presented a transitory viral load ≥50 copies/mL (blips) .

In the multivariate analysis of therapeutic failure in the lopinavir/ritonavir monotherapy group, adherence was not associated with therapy failure for the three definitions (all *P*>0.20). In the multivariate model, only older age at baseline (odds ratio, 1.09; 95% CI, 1.01 to 1.17) was associated with failure.

Genotypic analysis

Genotypic analysis was performed for patients with plasma HIV-1 RNA ≥50 copies/mL according to local measurement.

Thirty-nine blood samples (8 in the cART group, 31 in the lopinavir/ritonavir monotherapy group) from 27 patients (7 and 20, respectively) were sent to the central virology laboratory for genotyping testing. Retesting in the central laboratory yielded plasma HIV-1 RNA <50 copies/mL in 12 samples and 7 additional genotypes could not be determined. Therefore, 20 genotypes (14 patients, all in the lopinavir/ritonavir monotherapy group) could be analysed.

Eight patients had wild-type virus at the time of viral rebound. Five patients infected with non-B subtype HIV-1 had mutations that were present at baseline in PBMCs, probably reflecting a polymorphism in relation to subtype. One patient had a virus harbouring key mutations conferring resistance to indinavir at Week 48. These mutations had not been evidenced at baseline on DNA genotyping. No key mutation conferring resistance to lopinavir was selected.

Immunological changes

In the current cART group, median CD4 counts increased from 525 to 604 cells/mm^3 between baseline and Week 48 and in the lopinavir/ritonavir monotherapy group, from 494 to 592 cells/mm^3.

Lipids, body fat distribution and bone metabolism

Changes from inclusion to Week 48 in fasting triglycerides, total cholesterol, LDL-cholesterol, HDL-cholesterol and creatinine clearance were assessed. The only difference between treatment groups was fasting total cholesterol change, which was significantly higher in the lopinavir/ritonavir monotherapy group (+0.42 mmol/L) than in the current cART group (+0.08 mmol/L; $P=0.04$).

Seventy patients were included in the DEXA substudy. Their baseline characteristics were similar between treatment groups and comparable to the non-included patients for HIV infection and adiposity profile (data not shown). Among these 70 patients, 53 (42 males and 11 females) underwent both baseline and Week 48 DEXA measurements. In the subgroup of the 42 males (23 patients in the current cART group and 19 patients in the lopinavir/ritonavir group) the evolution of weight, trunk fat mass and bone mineral density at defined sites (lumbar spine, neck of femur, total hip) did not differ between the treatment groups. Fat mass in the legs increased significantly more in the lopinavir/ritonavir group than in the current cART group (Table 3). In the multivariate linear regression analysis, factors associated with the evolution of fat leg mass were: discontinuation of thymidine analogues (slope for 1 year: +0.54 kg; 95% CI, +0.19 to +0.89); and NNRTI versus lopinavir/ritonavir prior to randomization (slope for 1 year, +0.46 kg; 95% CI, +0.09 to +0.83). Interestingly, after adjustment for NRTI use, the randomization group and exposure to NNRTI versus exposure to lopinavir/ritonavir prior to inclusion were no longer significantly associated. Ethnic origin (black versus white people) was close to statistical significance (slope for 1 year, −0.39 kg; 95% CI, −0.80 to 0.03). Among the 11 female (8 in the current cART group, 3 in the lopinavir/ritonavir group) who underwent two DEXA measurements, evolution of bone mineral density, body mass index, truncal and peripheral fat mass were similar between treatment groups (all P values ≥ 0.35).

Treatment adherence

Overall, 87% of the questionnaires were completed by patients on treatment (83% in the current cART group, 91% in the lopinavir/ritonavir monotherapy group). At Weeks 12, 24, 36 and 48, 49%, 55%, 63% and 64% of patients in the current cART group were adherent to treatment as were 56%, 58%, 41% and 52% in the lopinavir/ritonavir monotherapy group. Overall, 59/93 (63%) patients in the current cART group were considered non-adherent on at least one visit versus 58/86 (67%) in the lopinavir/ritonavir monotherapy group. In addition, 29/93 (31%) on cART declared having missed at least one pill during the last 4 days on at least one visit versus 29/86 (34%) in the lopinavir/ritonavir monotherapy group and then 50/93 (54%) versus 52/86 (61%) declared having missed at least one pill during the last 4 weeks on at least one visit (respective P values 0.64, 0.75 and 0.45).

Safety

Twelve serious adverse events were reported during the study; none was considered related to study treatment. Grade 3–4 biological events were observed in three patients of the current cART group (total cholesterol and triglycerides increase, $n=1$; triglycerides increase, $n=2$) and in three patients of the lopinavir/ritonavir monotherapy group (total cholesterol increase, $n=1$; serum alanine aminotransferase (ALT) increase, $n=1$; serum aspartate aminotransferase (AST) and ALT increase, $n=1$; the increase in serum AST and ALT was related to acute hepatitis C). No patient experienced a creatinine clearance <30 mL/min during follow-up. Thirteen patients in the current cART group experienced at least one episode of diarrhoea versus 34 in the lopinavir/ritonavir group ($P<0.001$). Among

Table 3. Changes from baseline in soft tissue compartments and bone mineral density at Week 48 among 42 male patients, KALESOLO Study, 2005–08

Parameters	Median change (IQR) at Week 48		
	current cART group ($n=23$)	LPV/r monotherapy group ($n=19$)	P value[a]
Weight, kg	0 (−1 to 2)	0 (− to 2)	0.98
BMI, kg/m^2	0.11 (−0.6 to 0.92)	0.00 (−0.6 to 0.62)	0.66
Body fat measurements by DEXA, kg			
truncal fat	0.64 (−0.0 to 1.41)	0.47 (−0.7 to 1.56)	0.61
peripheral fat (lower limbs)	−0.05 (−0.6 to 0.25)	0.16 (−0.1 to 0.89)	0.023
Bone mineral density by DEXA, g/cm^2			
lumbar spine	−0.004 (−0.02 to 0.009)	−0.013 (−0.01 to 0.009)	0.86
neck of femur	−0.002 (−0.01 to 0.011)	−0.001 (−0.01 to 0.015)	0.81
total hip	0.002 (−0.01 to 0.017)	0.001 (−0.01 to 0.011)	0.60

BMI, body mass index; IQR, interquartile range; LPV/r, lopinavir/ritonavir.
[a]Wilcoxon rank sum test for current cART group versus LPV/r monotherapy group.

these 34 patients, 5 were on a lopinavir/ritonavir-containing regimen prior to inclusion.

Post-study follow-up

Long-term follow-up (up to Week 96) was proposed to the 182 patients who completed the Week 48 visit and 161 were enrolled. Twenty-one patients were not enrolled for the following reasons: patient refusal (*n*=5); change of medical centre (*n*=7); inclusion in another trial (*n*=5); medical decision (*n*=3); and pregnancy (*n*=1). Four visits were planned every 3 months between Weeks 48 and 96. Between the first and last long-term follow-up visits, three additional patients stopped their participation because of inclusion in another clinical trial. Therefore, 158 patients were followed up and plasma HIV-1 RNA determinations were available in 153 patients at Week 96 (75 in the cART group and 78 in the lopinavir/ritonavir monotherapy group). From Week 48 to Week 96, treatment modifications were reported in 34 patients (28 in the cART group and 6 in the lopinavir/ritonavir monotherapy arm). Among the 153 patients evaluated at Week 96, plasma HIV–1 RNA was ≥50 copies/mL in 3 patients (3/78) in the lopinavir/ritonavir monotherapy group and in 2 patients in the cART group (2/75).

At Week 96, 64/87 (74%) patients were still receiving monotherapy and 48/99 (48%) current treatment without any treatment change since the randomization. Plasma HIV-1 RNA was ≥50 copies/mL at Week 96 in three patients; two in the lopinavir/ritonavir monotherapy group (95 and 157 copies/mL) and one in the cART group (55 copies/mL).

Discussion

In the present study, a large proportion of patients achieved success at the end of the trial in both arms. Using a strict definition of virological control (plasma HIV-1 RNA <50 copies/mL) did not allow demonstration of the non-inferiority of a lopinavir/ritonavir monotherapy regimen in comparison with a current three-drug therapy in a population of virologically suppressed patients (−4.0%; 90% CI, −12.4% to 4.5%), whereas non-inferiority was demonstrated at an HIV-1 RNA cut-off of 400 copies/mL (−0.5%; 90% CI, −8.5% to 7.4%).

Of interest, if treatment intensification was not considered as failure, the non-inferiority hypothesis was achieved even with a definition of virological suppression of <50 copies/mL; 88% of patients were suppressed in the current cART group versus 91% of patients in the lopinavir/ritonavir monotherapy group. These two approaches are complementary; the 'switch equals failure' analysis, which does not allow treatment modifications, evaluates the intrinsic efficacy and safety profile of a fixed treatment and the 'switch included' analysis allows treatment modifications according to the clinical evolution and evaluates the long-term outcome.[19]

An important finding in our results is the potential benefit of the monotherapy strategy on lipoatrophy. The M03-613 and MONARK trials showed a significant improvement in peripheral lipoatrophy with the lopinavir/ritonavir simplification strategy.[20,21] We also observed an improvement in leg fat, but our results were limited to men. In the MONARK and M03-613 trials, all patients of the comparative groups received zidovudine; therefore, a lesser effect on lipoatrophy was expected in our

study since the comparative group was composed of a majority of patients receiving NRTIs known to have limited impact on metabolism and lipodystrophy (tenofovir DF, abacavir). Trunk fat accumulation did not differ between the two treatment arms. Among lipid parameters, only fasting total cholesterol increased significantly more in the lopinavir/ritonavir monotherapy group than in the current cART group.

Despite the high levels of controlled patients in lopinavir/ritonavir monotherapy studies (>80% of patients), patients in the lopinavir/ritonavir monotherapy group experienced virological fluctuations ≥50 copies/mL more frequently during the 48 week follow-up than patients in the reference arm. However, in our study, no new resistance mutation was observed during follow-up in the patients of the lopinavir/ritonavir monotherapy group and the increase in CD4 count was comparable in the two groups.

Safety was good despite the *de novo* use of lopinavir/ritonavir in two-thirds of patients of the lopinavir/ritonavir monotherapy group. This is a helpful result for clinical practice since other studies compared lopinavir/ritonavir monotherapy only with a lopinavir/ritonavir-containing regimen.

Long-term follow-up data support the value of this strategy with 60/87 patients still on monotherapy with maintained plasma HIV-1 RNA of <50 copies/mL at Week 96. The data at 4 years of the OK pilot study of lopinavir/ritonavir monotherapy confirm the long-tem efficacy and safety of this strategy (67% of patients remained on monotherapy at 4 years without treatment modification).[22]

The main limitation of this study is its open-label design. However, virological and immunological endpoints are most probably not biased by the absence of blinding. A second limitation is that not all subjects had DEXA scans because DEXA was available only in a limited number of centres. A third limitation is the imbalance of reasons for failure between treatment groups; failures due to virological failure (*n*=5) were more frequent in the current lopinavir/ritonavir group and missing viral loads (due to loss to follow-up) were more frequent in the current cART group (*n*=5). Whether this distribution between the two treatment groups was obtained simply by chance or for other reasons cannot be assessed on this small number of events.

Our results are in accordance with recent studies evaluating the efficacy of lopinavir/ritonavir monotherapy. To date, six randomized controlled clinical trials evaluating lopinavir/ritonavir monotherapy have been published (four in virologically suppressed patients and two in antiretroviral-naive patients).[14,15,23–26] In these six trials, the meta-analysis of Bierman *et al.*[27] showed that the risk of therapy failure was greater on lopinavir/ritonavir monotherapy; 121/364 (33.2%) patients versus 64/280 (22.9%) patients on cART (odds ratio, 1.48; *P*=0.037). If patients with successfully resuppressed HIV-1 RNA upon reintroducing NRTIs were not considered as failures, the risk of therapy failure did not differ; 98/364 (26.9%) versus 64/280 (22.9%) patients (odds ratio, 1.05; *P*=0.81).

The higher proportion of patients with episodes of low-level viraemia in comparison with classical three-drug regimens is a major concern for a simplification strategy with lopinavir/ritonavir monotherapy. One reason could be insufficient antiretroviral potency. Drug adherence might be an important factor for

virological fluctuations, particularly in patients on lopinavir/ritonavir monotherapy. Since lopinavir/ritonavir has a short terminal half-life, it is reasonable to postulate that patients missing doses of lopinavir/ritonavir monotherapy have a greater risk of virological rebound.[28]

In most studies, the low-level viraemia was not related to development of resistance mutations. In the MONARK trial, additional mutations that were not present at baseline were detected in the protease gene in 3 of 83 patients (3.6%) on lopinavir/ritonavir monotherapy. This latter trial was, however, performed in antiretroviral-naive patients and these mutations had a modest impact on lopinavir susceptibility.[26] It is reassuring to note that, as in our trial, the randomized arms showed a similar increase in CD4 count in patients receiving lopinavir/ritonavir monotherapy or triple combination regimens.[20,26] Despite higher rates of low-level viraemia in the lopinavir/ritonavir monotherapy groups, this suggests that low-level viraemia has minimal, if any, consequences on short-term restoration of immune function.

The causes of low-level viraemia remain unclear. Besides poor adherence, another explanation for low-level viraemia and increased failure in patients on lopinavir/ritonavir monotherapy could be the absence of HIV suppression in some anatomical compartments. This could be related to decreased drug penetration in anatomical sites such as the CNS or genital tract.[29] It could be argued that levels of HIV-1 RNA of 50–400 copies/mL in ~10% of patients is after all the 'virological cost' of such a simplification strategy. However, the consequences of low-level viraemia need to be carefully estimated since prolonged periods of low-level viraemia might favour the development of resistance mutations and chronic inflammation.

In conclusion, lopinavir/ritonavir monotherapy did not achieve non-inferiority versus cART for maintaining plasma HIV-1 RNA at <50 copies/mL. Nevertheless, the incidence of virological failure was low (mostly with HIV-1 RNA <400 copies/mL) and easily managed by treatment intensification.

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Author contributions

J.-L. M. and P.-M. G. were involved in the study design, patient recruitment and writing and reviewing the manuscript, V. B. and G. C. performed the statistical analyses and were involved in the study design, statistical writing and reviewing the manuscript, R. L. and P. M. were involved in the study design, patient recruitment and reviewing the manuscript, P. B., V. B. and A. C. were involved in patient recruitment and reviewing the manuscript and S. K., J. I. and A.-M. T. were involved in the study design and reviewing the manuscript.

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