A Switch in Therapy to a Reverse Transcriptase Inhibitor Sparing Combination of Lopinavir/Ritonavir and Raltegravir in Virologically Suppressed HIV-Infected Patients: A Pilot Randomized Trial to Assess Efficacy and Safety Profile: The KITE Study

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Abstract

A nucleoside reverse transcriptase inhibitor (NRTI) backbone is a recommended component of standard highly active antiretroviral therapy (sHAART). However, long-term NRTI exposure can be limited by toxicities. NRTI class-sparing alternatives are warranted in select patient populations. This is a 48-week single-center, open-label pilot study in which 60 HIV-infected adults with plasma HIV-1 RNA (<50 copies/ml) on sHAART were randomized (2:1) to lopinavir/ritonavir (LPV/r) 400/100 mg BID + raltegravir (RAL) 400 mg BID switch (LPV-r/RAL arm) or to continue on sHAART. The primary endpoint was the proportion of subjects with HIV-RNA <50 copies/ml at week 48. Secondary efficacy and immunologic and safety endpoints were evaluated. Demographics and baseline lipid profile were similar across arms. Mean entry CD4 T cell count was 493 cells/mm³. At week 48, 92% [95% confidence interval (CI): 83–100%] of the LPV-r/RAL arm and 88% (95% CI: 75–100%) of the sHAART arm had HIV-RNA <50 copies/ml ($p=0.70$). Lipid profile (mean $\pm$ SEM, mg/dl, LPV-r/RAL vs. sHAART) at week 24 was total-cholesterol 194 ± 5 vs. 176 ± 9 ($p=0.07$), triglycerides 234 ± 30 vs. 133 ± 27 ($p=0.003$), and LDL-cholesterol 121 ± 6 vs. 110 ± 8 ($p=0.27$). There were no serious adverse events (AEs) in either arm. Regimen change occurred in three LPV-r/RAL subjects ($n=1$, due to LPV-r/RAL-related AEs) vs. 0 in sHAART. There were no differences between arms in bone mineral density, total body fat composition, creatinine clearance, or CD4 T cell counts at week 48. In virologically suppressed patients on HAART, switching therapy to the NRTI-sparing LPV-r/RAL combination produced similar sustained virologic suppression and immunologic profile as sHAART. AEs were comparable between arms, but the LPV-r/RAL arm experienced higher triglyceridemia.

Introduction

A STANDARD FIRST LINE HIGHLY active antiretroviral therapy (HAART) regimen consists of a backbone of two nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs) combined with a nonnucleoside reverse transcriptase inhibitor (NNRTI), or a boosted protease inhibitor (PI), or an integrase inhibitor.^{1–3} HAART has revolutionized human immunodeficiency virus (HIV) disease management, and life expectancy for many HIV-infected individuals on therapy

now approaches that of the general population.^{4–7} This unprecedented success of HAART is tempered, however, by the reality that antiretroviral therapy is life-long, and the beneficial effect of which can be variable. The long-term use of HAART has been fraught with drawbacks such as treatment-limiting toxicities, short-term durability, and suboptimum genetic barrier to the emergence of drug resistance for established agents.^{1,8–10} More specifically, therapy with the NRTI class has been limited by mitochondrial toxicity, renal impairment, hypersensitivity reaction, and discordant CD4⁺ T

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cell responses.^{11–14} Because of these limitations and the recent availability of newer classes of antiretroviral drugs, NRTI-sparing HAART regimens are increasingly being investigated as therapeutic alternatives for selected groups of patients intolerant to this antiretroviral class. PIs with or without ritonavir (RTV) boosting in combination with raltegravir (RAL), a first in class integrase inhibitor, is one such consideration, but the efficacy and safety profiles of many of these types of combinations are either untested or have been discouraging.¹⁵ In addition, unexpected drug–drug interactions are often a concern whenever novel combinations of drugs are coadministered.

In light of the aforementioned considerations, the combination of lopinavir/ritonavir (LPV/r) and RAL has been proposed as a potential NRTI class sparing alternative for a number of reasons. RAL is a safe and extremely potent antiviral compound with proven clinical efficacy in both treatment-naïve and treatment-experienced HIV-infected patients.^{16–19} However, virologic failure with rapid evolution of high-level resistance occurs when RAL is administered without effective backbone antiretroviral agents, raising concerns about its genetic barrier to resistance.^{20–22} LPV/r, on the other hand, maintains high plasma trough concentrations of lopinavir (LPV) that far exceed the EC₅₀ (concentration required for 50% of maximum effect) for many viral strains.^{23,24} This high level of drug exposure provides a pharmacologic barrier to the emergence of viral resistance as well as enhanced activity against certain resistant viral strains.^{25,26} Furthermore, RAL is metabolized primarily by uridine diphosphate glucuronosyltransferase (UGT) 1A1²⁷ and does not influence the activities of the cytochrome P450 enzyme system²⁸; therefore, a significant drug–drug interaction with LPV/r due to enzymatic induction or inhibition is not anticipated.¹⁹ The pharmacokinetic profiles of LPV/r and RAL also permit paring in a manner that provides compatible dosing symmetry of twice-daily administration.^{29,30} Thus, the LPV-r/RAL pairing may prove to be an effective alternative HAART regimen that offers a comparatively higher genetic barrier to the emergence of resistant mutants in addition to producing an enhanced and durable antiviral efficacy void of the treatment-limiting drawbacks of the NRTI class.

We therefore hypothesized that a switch from a standard HAART (sHAART) regimen consisting of at least two NRTIs to an NRTI-sparing combination of LPV/r and RAL would be as efficacious and as tolerated as continuing therapy with sHAART. The Kaletra-Isentress Treatment Evaluation (KITE) study is thus a pilot study designed to assess the efficacy and safety profile of the combination of the NRTI-sparing LPV/r and RAL (LPV-r/RAL) in antiretroviral treated, virologically suppressed HIV-1-infected individuals.

Materials and Methods

Study design and population

The KITE study was a prospective, open-label, two-arm randomized controlled exploratory trial conducted in a population of HIV-infected subjects who had been on an sHAART regimen that included two NRTIs for ≥ 6 months. All subjects were recruited from an urban outpatient HIV clinic (the Grady Infectious Diseases Program Out-patient Clinic, Atlanta, Georgia) between June 2008 and January 2011. Additional eligibility criteria included male and female subjects

age ≥ 18 years old, undetectable plasma HIV-1 RNA level (< 50 copies/ml), and absence of a history of virologic failure to a PI-based HAART regimen. Subjects were not enrolled if they were on medications that could interact with PIs, on investigational antiretroviral agents, had an active opportunistic infection, had renal and/or hepatic impairment, or were pregnant. Hepatitis B virus (HBV)-coinfecting patients receiving a nucleotide analogue for both HIV and HBV suppression were also excluded from enrollment. Sexually active females were required to have a negative pregnancy test and use barrier contraception during the study.

At enrollment, demographic information, medication history, and clinical and laboratory data were collected. Baseline plasma HIV-1 RNA level, CD4 T cell counts, fasting lipid profile, and dual energy x-ray absorptiometry (DXA) for total body fat distribution and bone mineral density (BMD) were performed. Subjects were randomized in a 2:1 fashion to switch to an antiretroviral regimen containing LPV/r 400/100 mg + RAL 400 mg, both administered orally twice daily (LPV-r/RAL, arm 1) or to continue therapy with their pre-study NRTI-containing HAART regimen (sHAART, arm 2) using permuted-block randomization. Antiretroviral adherence counseling was provided to all subjects.

Follow-up visits occurred at weeks 2, 4, 8, 16, 24, 36, and 48, during which plasma HIV-1 RNA levels, CD4 T cell counts, comprehensive metabolic panels (including serum electrolyte levels and liver function tests), and complete blood cell counts with differential and platelets were performed. Fasting lipid profiles were repeated at weeks 24 and 48, and DXA scans at week 48. Safety was assessed at seven postrandomization scheduled visits at weeks 2, 4, 8, 16, 24, 36, and 48 by evaluating, grading, and recording self-reported adverse events (AEs) experienced by subjects. AEs were graded for severity via the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (http://rcc.tech-res.com/tox_tables.htm). Study drugs were discontinued for an AE at the discretion of the study clinical investigators. Treatment adherence assessment using a previously validated self-administered adherence questionnaire³¹ was also performed at each study visit. Subjects who experienced virologic rebound during the study period (defined as detectable plasma HIV-1 RNA level > 400 copies/ml on two consecutive samples drawn at least 2 weeks apart) were evaluated with an HIV-1 genotype and for change in antiretroviral therapy. All subjects provided written informed consent before undergoing any study procedures. This study (NCT00700115) was designed according to the ethical guidelines for human studies and approved by the Institutional Review Board of Emory University.

Statistical analysis

The primary analyses of the data were performed according to subjects' original treatment assignment (i.e., intention-to-treat analyses) and all data from all subjects randomized were included in the final analysis. Demographic and clinical characteristics were compared between treatment arms with the two-sample *t*-test for continuous variables and with a chi-square test or Fisher's exact test for proportions. The percentage of patients with undetectable plasma viral load (HIV-1 RNA < 50 copies per ml) was determined at the time of randomization and at weeks 2, 4, 8, 16, 24, 36, and 48 and

FIG. 1. Consort diagram of the progress through the phases (enrollment, treatment allocation, follow-up, and data analysis) of a parallel randomized trial of two arms [the lopinavir/ritonavir (LPV/r) 400/100 mg BID + raltegravir (RAL) 400 mg BID switch or continue standard highly active antiretroviral therapy (sHAART)].

compared between the LPV-r/RAL and sHAART arms by performing a generalized estimating equations (GEE) analysis using SAS Proc Genmod with an exchangeable correlation structure for the repeated measures within the participant (binomial-logit model). The statistical model provided estimates of the percentages of virologically suppressed patients by treatment arm and time on study. The model-based estimates are unbiased with unbalanced and missing data, so long as the missing data are noninformative (missing completely at random). A p value ≤ 0.05 was considered statistically significant for the main effects (treatment and time on study) and interaction term (treatment arm by time on study) from the repeated measures analysis. Time cumulative event-free treatment failure (i.e., virologic failure defined as time on study until the first of two consecutive HIV-1 RNA levels >400 copies/ml measured at least 2 weeks apart or antiretroviral regimen change), the earliest event relative to randomization date was estimated by the Kaplan–Meier method. Patients without virologic failure or regimen change were censored at the date of last follow-up. Event-free treatment failure rates between the LPV-r/RAL and sHAART arms were compared with a log-rank test.

Repeated-measures analyses using mixed linear models for immunologic response data (CD4 and CD8 T cell counts), fasting lipid profile data (total cholesterol, triglycerides, LDL, and HDL), creatinine clearance (CrCL), and DXA-scan for total fat distribution and BMD were done with a means model using SAS Proc Mixed providing separate estimates of the means by study week and treatment arm. An unstructured variance-covariance form among the repeated measurements was assumed for each outcome and estimates of the standard errors of parameters were used to perform statistical tests and construct 95% confidence intervals (CI). The model-based means

are unbiased with unbalanced and missing data, so long as the missing data are noninformative (missing at random). Missing values were assumed missing at random, i.e., conditional on the observed data the missing responses are independent of the unobserved responses. Statistical tests were two-sided. A p value ≤ 0.05 was considered statistically significant for the main effects and interaction term (treatment arm by time on study) from the repeated measures analysis for each outcome. An adjusted mean was calculated for each outcome for each treatment arm. The adjusted mean for each treatment arm was defined as the predicted mean response obtained by evaluating the statistical model at the mean baseline value for the two treatment arms. Analysis of covariance (ANCOVA) was used to adjust for any baseline differences between treatment arms when estimating the 48-week adjusted mean for CD4 T cells and CD8⁺ T cells and 24-week adjusted mean for total cholesterol, triglycerides, HDL, and LDL.

Each of 33 solicited AEs was counted only once per patient as the most severe level reported and was aggregated across severity (mild, moderate, severe) and time on study and compared between treatment arms using a chi-square test or Fisher's exact test. Statistical analyses were limited to the 10 most commonly reported AEs after excluding those symptoms reported as mild.

Results

Disposition of patients

The sample of enrollees randomized to LPV-r/RAL ($n=40$) or to continue sHAART ($n=20$) was derived from 166 individuals assessed for eligibility (Fig. 1). Demographic data, baseline clinical characteristics, and prestudy antiretroviral therapy regimens are presented in Table 1. With the exception

TABLE 1. BASELINE CHARACTERISTICS, ANTIRETROVIRAL REGIMEN, AND CLINICAL LABORATORY VALUES

	LPV-r/RAL (n=40)	sHAART (n=20)	p value
Male sex	26 (65%)	12 (60%)	0.77
Race			
African-American	31 (78%)	19 (95%)	0.14
White	9 (23%)	1 (5%)	
Others	0 (0%)	0 (0%)	
Age, years	46 (9)	48 (12)	0.25
BMI	29 (7)	28 (6)	0.64
HIV-RNA <50 copies/ml	35 (88%)	19 (95%)	0.65
CD4 T cell counts (cells/ μ l)	484 (306) ^a	512 (276)	0.72
CD8 T cell counts (cells/ μ l)	904 (545) ^a	784 (363)	0.38
Antiretroviral at entry			
LPV/r-based	16 (40%)	8 (40%)	1.00
PI-based (other than LPV/r)	8 (20%)	3 (15%)	0.88
NNRTI-based	15 (38%)	7 (35%)	1.00
TDF-containing	21 (53%)	13 (65%)	0.41
Creatinine clearance ^b (ml/min)	122 (47)	100 (27)	0.05
AST/SGOT (U/liter)	30 (17)	32 (16)	0.56
ALT/SGPT (U/liter)	30 (32)	33 (30)	0.80
Total cholesterol (mg/dl)	179 (30)	184 (41)	0.55
Triglycerides (mg/dl)	141 (88)	145 (94)	0.88
HDL cholesterol (mg/d)	47 (16)	49 (16)	0.58
LDL cholesterol (mg/d)	114 (28)	121 (47)	0.44
On lipid-lowering agent	10 (25%)	4 (20%)	1.00

^aTotal *n* for whom data are available=39.

^bCalculated by Cockcroft-Gault equation.

Data are number (%) or mean (SD).

LPV/r, lopinavir/ritonavir; RAL, raltegravir; sHAART, standard highly active antiretroviral therapy; BMI, body mass index; AST/SGOT, aspartate aminotransferase; ALT/SGPT, alanine aminotransferase; PI, protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor.

of CrCL, which was higher in the LPV-r/RAL arm, there were no statistically significant differences between the two arms for the other characteristics. Plasma HIV-1 RNA level was <50 copies/ml for all subjects at screening, and for 54 subjects at entry. For the remaining six subjects (five in LPV-r/RAL arm and one in the sHAART arm), the entry HIV-1 RNA was detectable, but the level was <100 copies/ml (with exception of one subject in the LPV-r/RAL arm with a value of 550 copies/ml). Five of these subjects with low level viremia at entry had undetectable plasma HIV-1 RNA levels at the week 48 visit.

Prestudy HAART treatment

The median time on the most recent HAART regimen prior to study entry was comparable between the two groups (3.4 years for LPV-r/RAL and 4.3 years for sHAART, *p*=0.64) as was the number of prestudy regimens (one for LPV-r/RAL and two for sHAART, *p*=0.26). At baseline, 13% (5/40) in the LPV-r/RAL arm and 10% (2/20) in the sHAART arm were on RTV-boosted HAART regimens other than LPV/r. Of those that were on a PI-based HAART regimen prior to study entry, in 16 out of 40 (40%) in the LPV-r/RAL arm and in 8 out of 20 (40%) in the sHAART arm, the regimen included LPV/r. Thirty-eight percent (15/40) of subjects in the LPV-r/RAL arm and 35% (7/20) in the sHAART arm were on an NNRTI-based regimen at baseline. The prestudy HAART regimen included tenofovir disoproxil fumarate (TDF) in 53% (21/40) of subjects in the LPV-r/RAL arm and 65% (13/20) in the sHAART arm (*p*=0.41).

Virological response

The percentage of patients with undetectable plasma viral loads (HIV-1 RNA <50 copies/ml) was similar between the two study arms during the 48 weeks of follow-up (*p*=0.87, test for interaction between time on study and treatment group; Fig. 2A). Over the 48-week study period, the estimated percentage of patients that had HIV-1 RNA <50 copies/ml was 92.7% (95% CI: 83–100%) for the LPV-r/RAL arm and 88% (95% CI: 75–100%) for the sHAART arm (*p*=0.70). At week 48, 91.7% (95% CI: 83–100%) of patients on the LPV-r/RAL-arm had HIV-1 RNA <50 copies per ml compared with 88.2% (95% CI: 75–100%) of patients on the sHAART arm (*p*=0.70). Among patients who completed follow-up, virologic suppression (HIV-1 RNA <50 copies/ml) at week 48 was achieved by 32 of 35 patients (91%) in the LPV-r/RAL arm compared with 16 of 18 patients (89%) in the sHAART arm.

Figure 2B summarizes the cumulative percentage of patients without virological failure and/or a regimen change by treatment group. Forty-eight week cumulative likelihood of remaining free of treatment failure was 92.4% for the LPV-r/RAL treatment group compared with 90.0% for the sHAART treatment group (*p*=0.77, log-rank test).

A total of six treatment failures were observed, four in the LPV-r/RAL arm and two in the sHAART arm. In the LPV-r/RAL arm, the reason for treatment failure was regimen change in three subjects; one had study drug-related intractable itching, another had palpitation and near-syncope experience (after self-medication with over-the-counter cold medication) that was judged not to be study drug related, and

FIG. 2. Longitudinal changes in the percentages of patients with undetectable plasma viral load (HIV-RNA <50 copies per ml) by treatment arm (A). The time-trend lines are the model-based estimates obtained from a generalized estimating equations analysis of repeated binary responses within patients. The vertical bars are the 95% confidence intervals. The numbers provided at the bottom of the plot indicate the number of patients with data at each time point. (B) Estimates of the cumulative percentage of patients without virologic failure or a regimen change (event-free treatment failure) by treatment group ($p=0.77$, log-rank test). The numbers provided at the bottom of the plot indicate the number of patients that remain at risk.

the last discontinued for personal reason. The only virologic failure in the LPV-r/arm occurred at the final week 48 follow-up visit (plasma HIV-1 RNA = 22,320 copies/ml); the patient could not be reached to confirm this result. The two treatment failures in the sHAART group were due to confirmed virologic failure. All three virologic failures in the study population (one in the LPV-r/RAL arm and two in the sHAART arm) occurred in the setting of nonadherence (subjects' self-discontinuation of the study drug).

Immunological response

Statistically, CD4 T cell counts in the two treatment arms changed in significantly different ways during follow-up ($p=0.049$, test for interaction between time on study and treatment group; Fig. 3E). However, even though mean CD4 T cell counts were similar in both arms at the time of randomization, the mean CD4 T cell counts became higher in the sHAART arm at week 4 compared with the LPV-r/RAL arm

(mean $\pm$ SEM: 610 ± 83 cells/ μ l versus 470 ± 44 cells/ μ l, $p=0.14$). At week 48, mean CD4 T cell counts for the sHAART and LPV-r/RAL arms were similar (576 ± 63 cells/ μ l versus 519 ± 35 cells/ μ l, $p=0.42$, respectively). The week 48 CD4 T cell counts mean adjusted for baseline was 535 ± 23 cells/ μ l and 574 ± 33 cells/ μ l for the LPV-r/RAL and sHAART arms, respectively ($p=0.35$, Table 2).

Adherence to study regimen

Adherence data were collected by self-report for 59 patients (one LPV-r/RAL patient withdrew consent on the date of randomization and therefore adherence data could not be collected). Overall, patients in both arms tended to report a high degree of adherence to the study regimen. In response to the following question: During the past 4 days, on how many days have you missed taking all your doses: none, 1 day, 2 days, 3 days, or 4 days, the 20 sHAART patients (129 clinical visits) self-reported missing no doses 77.4% of the time and

FIG. 3. Longitudinal changes in mean total cholesterol (mg/dl; **A**), triglycerides (mg/dl; **B**). Triglycerides were significantly higher in the lopinavir/ritonavir-raltegravir (LPV-r/RAL) group at 24 weeks ($p=0.05$) but not at week 48 ($p=0.61$), HDL (mg/dl; **C**), LDL (mg/dl; **D**), CD4 T cell count (cells/mm³; **E**), and creatinine clearance (ml/min; **F**) by treatment arm. The time trend lines are the model-based means obtained from a repeated-measures analysis. The vertical bars are the 95% confidence intervals.

the 39 LPV-r/RAL patients (264 clinical visits) reported missing no doses 93.5% of the time during the 48 weeks of follow-up ($p=0.009$). Rates of not missing any doses by self-report were consistent across visits ($p=0.82$, test for interaction between treatment group and study visit). An adherence score was calculated for each patient at each visit on an ordinal scale (4=missed all doses over the past 4 days, 3=missed 3 days, 2=missed 2 days, 1=missed 1 day, and 0=none). The mean adherence score was 0.32 for the sHAART arm and 0.06 for the LPV-r/RAL arm ($p=0.002$) suggesting better adherence for the LPV-r/RAL arm. Similar results were found when asked "When was the last time you missed any of your medications: never skip medications,

more than 3 months ago, 1–3 months ago, 2–4 weeks ago, within the past week" (data not shown).

Safety profile

Fasting lipid profile (baseline vs. week 24; and vs. week 48). Both total cholesterol and triglycerides for the cohort were statistically significantly increased during the follow-up periods ($p=0.008$ for total cholesterol and $p=0.008$ for triglycerides, test for the interaction between time on study and treatment group; Fig. 3A and B). Mean total cholesterol was similar in both treatment arms at baseline ($p=0.56$) but became higher in LPV-r/RAL patients at week 24 (176 mg/dl

TABLE 2. SUMMARY STATISTICS FOR SECONDARY OUTCOMES BY TREATMENT GROUP ADJUSTING FOR BASELINE CHARACTERISTICS USING ANALYSIS OF COVARIANCE

	Treatment	n	Adjusted mean $\pm$ SEM ^a	Difference between Means (95% CI)	p ^b
Total cholesterol (mg/dl)	LPV-r/RAL	35	194.0 $\pm$ 4.3	-21.9 (-36.5, -7.2)	0.004
	sHAART	19	172.1 $\pm$ 5.8		
Triglycerides (mg/dl)	LPV-r/RAL	35	238.1 $\pm$ 19.9	-104.8 (-172.6, -37.0)	0.003
	sHAART	19	133.3 $\pm$ 27.1		
HDL cholesterol (mg/dl)	LPV-r/RAL	35	50.7 $\pm$ 2.8	-3.7 (-13.2, 5.9)	0.45
	sHAART	19	47.1 $\pm$ 3.8		
LDL cholesterol (mg/dl)	LPV-r/RAL	35	121.1 $\pm$ 5.6	-13.0 (-32.0, 5.9)	0.17
	sHAART	19	108.0 $\pm$ 7.6		
Creatinine clearance ^c (ml/min)	LPV-r/RAL	33	106.1 $\pm$ 4.2	9.7 (-4.7, 24.2)	0.18
	sHAART	18	115.9 $\pm$ 5.8		
CD4 T cell counts (cells/ μ l)	LPV-r/RAL	35	535.2 $\pm$ 23.3	38.5 (-42.6, 119.6)	0.35
	sHAART	17	573.7 $\pm$ 32.9		
CD8 T cell counts (cells/ μ l)	LPV-r/RAL	35	879.6 $\pm$ 33.0	34.6 (-80.6, 149.9)	0.55
	sHAART	17	914.3 $\pm$ 46.7		

^aAdjusted means calculated at week 48 for CD4 T cell counts, CD8 T cell counts, and creatinine clearance. All others calculated at week 24.

^bp value comparing the two adjusted means.

^cCalculated by Cockcroft-Gault equation.

and 194 mg/dl for sHAART and LPV-r/RAL, respectively; $p=0.07$; mean difference = 18 mg/dl). Similarly the mean triglyceride level was not significantly different in both treatment arms at baseline ($p=0.88$) but became higher in LPV-r/RAL patients at week 24 (153 mg/dl and 234 mg/dl for sHAART and LPV-r/RAL, respectively; $p=0.05$; mean difference = 80 mg/dl). Triglycerides increased from baseline to weeks 24 and 48, respectively, by 6% and 11% in sHAART patients and 66% and 27% in LPV-r/RAL patients. The week 24 triglyceride mean adjusted for baseline was 133 mg/dl and 238 mg/dl for the sHAART and LPV-r/RAL arms, respectively ($p=0.003$, Table 2). Mean HDL and LDL levels were similar for the two treatment arms through the follow up period ($p=0.44$ and $p=0.67$, respectively; Fig. 3C and D). The proportion on lipid-lowering agents at study entry was comparable between the two cohorts, 25% (10/40) in the LPV-r/RAL arm versus 20% (4/20) in the sHAART arm ($p=1.00$). Lipid-lowering therapy was initiated during the study in one patient in the LPV-r/RAL arm.

Renal function. The baseline mean CrCL was statistically significantly higher for LPV-r/RAL patients compared to sHAART patients ($p=0.02$; Fig. 3F). From baseline to week 2, the mean CrCL declined from 120 ml/min to 111 ml/min in the LPV-r/RAL arm and increased slightly from 100 ml/min to 104 ml/min in the sHAART arm. From baseline to week 48, the mean CrCL rose from 100 ml/min to 106 ml/min ($p=0.15$) in the sHAART arm, but decreased slightly from 122 ml/min to 116 ml/min ($p=0.18$) in the LPV-r/RAL arm; week 48 mean CrCL was not significantly different between arms ($p=0.37$). The week 24 mean CrCL adjusted for baseline was 106 ml/min and 116 ml/min for the sHAART and LPV-r/RAL arms, respectively ($p=0.18$, Table 2). Among 28 subjects whose baseline sHAART regimen included TDF ($n=17$ in LPV-r/RAL and $n=11$ in sHAART), baseline adjusted CrCL (mean $\pm$ SEM) in the sHAART and LPV-r/RAL arms, respectively, was 107 $\pm$ 4 ml/min and 114 $\pm$ 5 ml/min (week 2), 107 $\pm$ 4 ml/min and 114 $\pm$ 5 ml/min (week 24), and 111 $\pm$ 6 ml/min and 117 $\pm$ 7 ml/min (week 48), and did not significantly differ between arms. Seven (41%) of the 17 pa-

tients on TDF at baseline who switched to LPV/RTV-RAL had a decrease in CrCL at 48 weeks.

Body fat composition and bone mineral density by DXA-scan (baseline vs. week 48). Figure 4 summarizes longitudinal change in DXA scan measurements by treatment arm. No difference between treatments arms over time was significant for total body fat ($p=0.60$), trunk fat ($p=0.72$), arm fat ($p=0.93$), and leg fat ($p=0.72$). Similarly, no difference between treatments arms over time was significant for total BMD ($p=0.50$), pelvis BMD ($p=0.56$), or spine BMD ($p=0.72$).

Adverse events

There were no serious AEs during the study. Table 3 summarizes patient reported AEs by treatment arm. Moderate or severe diarrhea was reported by 10 patients over the 48-week study period in the LPV/r+RAL group and by one patient in the sHAART group ($p=0.08$). Moderate or severe myalgia was more frequent in the sHAART group compared to the LPV/r+RAL group ($p=0.002$). There were no statistically significant differences between the two treatment groups for the other eight self-reported AEs (Table 3). A grade 3 fasting glucose elevation (>251 but less than 500 mg/dl) was observed in one sHAART patient and in two LPV-r/RAL patients, all of whom had preexisting diabetes mellitus. No $\geq$ grade 3 toxicities were observed during follow-up for hemoglobin, platelet count, ALT, AST, creatinine, and cholesterol.

Discussion

The findings of the KITE study provide preliminary evidence of the efficacy and safety of the novel NRTI-sparing combination of LPV-r/RAL. It raises the profile of this combination as a potential alternative regimen, particularly for individuals who are intolerant of the NRTI class of drug, and for whom a boosted PI regimen, such as LPV/r, is considered a suitable option. Virologic suppression was maintained at a reassuring rate of 92% for the LPV-r/RAL arm through the 48-week follow-up period. The paradigm of novel class-sparing regimens with comparable efficacy and/or tolerability profile

FIG. 4. Longitudinal changes in mean body fat composition (total fat (kg; **A**), trunk fat (kg; **B**), arm fat (kg; **C**), leg fat (kg; **D**), and bone mineral density (pelvis density, g/cm²; **E** and spine density g/cm²; **F**) by treatment arm. The time trend lines are the model-based means obtained from a repeated-measures analysis. The vertical bars are the 95% confidence intervals.

as established regimens is being entertained and evaluated in clinical trials.^{32,33} Recent publications on class-sparing antiretroviral switch strategies have focused mostly on the replacement of the PI anchor of the regimen with RAL rather than on the NRTI backbone substitution.^{32,33} Furthermore, evaluations of RAL/PI-based, NRTI class-sparing regimens are mostly being conducted in treatment-naïve settings as in the PROGRESS study with LPV-r/RAL, the SPARTAN study with atazanavir (ATV)/RAL,¹⁵ and the ACTG 5262 study with darunavir (DRV/RTV)/RAL.^{34,35} Data from these treatment-naïve studies are currently limited to preliminary reports presented at scientific forums. Nevertheless, the virologic outcome in the KITE study is comparable in magnitude to that observed in the RAL-containing SPIRAL switch

study where the PI component was replaced by RAL.³³ This suggests that when RAL is used in a switch therapy, substituting the NRTI backbone with a pharmacologically enhanced potent PI such as LPV/r could be as efficacious in maintaining virologic suppression as replacing the PI component. Encouragingly, corroborative observation is being made in the treatment-naïve setting of the PROGRESS study where the virologic efficacy of the NRTI-sparing LPV-r/RAL combination was noted to be similar to that of tenofovir disoproxil fumarate (TDF)/entricitabine (FTC) plus LPV/r.³⁶

Although RAL is a very potent antiretroviral agent, given the concern for low genetic barrier to evolution of drug resistance strains associated with its use, companion drug(s) with this agent in a combination therapy should ideally be

TABLE 3. SELF-REPORTED 10 MOST COMMON ADVERSE EVENTS BY TREATMENT GROUP

Symptom	LPV-r+RAL (n=40)	sHAART (n=20)	P-value
Diarrhea	10 (25%)	1 (5%)	0.08
Insomnia	4 (10%)	2 (10%)	1.00
Arthralgia	3 (8%)	3 (15%)	0.39
Flatulence	4 (10%)	1 (5%)	0.66
Rash	4 (10%)	1 (5%)	0.66
Decreased libido	4 (10%)	1 (5%)	0.65
Cough	4 (10%)	1 (5%)	0.65
Myalgia	0 (0%)	5 (25%)	0.002
Abdominal pain	3 (8%)	2 (10%)	1.00
Nausea	4 (10%)	0 (0%)	0.29

Data are number (%). All adverse events (AEs) were moderate or severe.

equally potent, active against diverse strains of viruses, and have dosing symmetry with RAL. In this regard, a LPV/r anchor seem compatible, as both drugs are administered twice daily, a factor that has been shown to enhance adherence.³⁷ Furthermore, the high plasma and presumably tissue exposures attained with standard dose of LPV/r^{23,24} offer broad antiviral activity against a wide range of viral strain^{25,26} and provide effective pharmacologic support for companion agents. These factors may have contributed to the unprecedented high level of adherence (94% in the LPV-r/RAL arm) and the virologic efficacy of this regimen in the current study as well as in another setting where it has been evaluated.³⁶

Another factor that may have contributed to the successful virologic outcome in this study is the duration of virologic suppression prior to study entry. Longer duration of viral suppression prior to therapy switch has been reported to be associated with lower risk of virological failure.^{23,24} In the KITE study all subjects were virologically suppressed for at least 6 months prior to study entry. Although the exact duration of virologic suppression before entry was not captured, the median duration on the most recent preentry HAART regimen was 3.4 years for the LPV-r/RAL arm and 4.3 years for the sHAART arm. Furthermore, the possibility of pre-existing resistance mutations to the study regimen was minimized by the exclusion of subjects with a history of prior PI resistance and/or treatment failure, or previous exposure to the integrase inhibitor class, factors that were shown to compromise treatment outcomes in the SWITCHMRK study.³²

Immunologic status was preserved through week 48 in the KITE study, with no clinically significant within-group or between-group differences in CD4 T cell counts changes from baseline to week 48. Though not consistently, switching to a RAL-containing regimen has been reported to induce increases in CD4 T cell counts compared with patients who remained on the same treatment regimen.^{16,38,39} Such an increase was not observed in the KITE study.

Overall, treatment failure, a composite outcome of treatment discontinuation for any reason including confirmed virologic failure, was encouragingly low in the KITE study, and mostly adherence related, with only one individual discontinuing LPV-r/RAL due to study drug-related AEs. The 48 weeks cumulative likelihood of remaining free of treatment failure was 92% in the LPV-r/RAL arm and 90% in the

sHAART arm. Although the study population was different, the safety profile of LPV-r/RAL in the KITE study closely mirrors that reported for the same regimen in the PROGRESS study, where the treatment discontinuation rate for any reason was 8%.³⁶ Three of the four treatment failures in the LPV-r/RAL arm of the KITE study were due to treatment discontinuation, but in only one subject (with intractable itching) was this judged to be related to the study drug.

There were no significant differences in bone mineral density, total body fat composition, and CrCL between arms throughout the 48 weeks follow-up. None of the self-reported 10 most common moderate to severe antiretroviral-related AEs in the LPV-r/RAL vs. sHAART arms led to treatment discontinuation. As was anticipated, switching to an RTV boosted regimen of LPV-r/RAL was associated with increases in fasting plasma total cholesterol, triglyceride, and LDL-cholesterol levels at 24 weeks, but only the increase in triglyceride level was statistically significant. In only 1 of 40 subjects in the LPV-r/RAL arm, was the change in lipid profile high enough to necessitate institution of a lipid-lowering agent. Consequently, the fasting lipid profile at the completion of the study was comparable between the arms.

The findings of the KITE study should be interpreted in the context of a pilot study with a small sample size; a larger definitive study with adequate power would be needed to validate our observations. Furthermore, AEs were self-reported, and the lack of blinding may have introduced biases in the collection of the data. In summary, these limitations notwithstanding, our data suggest that in patients with undetectable plasma HIV-1 RNA, switching therapy to the novel NRTI class-sparing LPV-r/RAL combination produced similar sustained virologic suppression and immunologic profile as sHAART. None of the top 10 self-reported AEs was severe enough to require treatment discontinuation, but the LPV-r/RAL arm experienced higher plasma triglyceride levels.

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Author Disclosure Statement

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