Sustained Antiretroviral Effect of Raltegravir After 96 Weeks of Combination Therapy in Treatment-Naive Patients With HIV-1 Infection

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Objectives: The purpose of this study was to evaluate the safety and efficacy of raltegravir vs efavirenz-based antiretroviral therapy after 96 weeks in treatment-naive patients with HIV-1 infection.

Methods: Multicenter, double-blind, randomized study of raltegravir (100, 200, 400, or 600 mg twice a day) vs efavirenz (600 mg every day), both with tenofovir/lamivudine (TDF/3TC), for 48 weeks, after which raltegravir arms were combined and all dosed at 400 mg twice a day. Eligible patients had HIV-1 RNA ≥5000 copies per milliliter and $CD4^+$ T cells ≥100 cells per microliter.

Results: One hundred ninety-eight patients were randomized and treated; 160 received raltegravir and 38 received efavirenz. At week 96, 84% of patients in both groups achieved HIV-1 RNA <400 copies per milliliter; 83% in the raltegravir group and 84% in the efavirenz group achieved <50 copies per milliliter (noncompleter = failure). Both groups showed similar increases in $CD4^+$ T cells (221 vs 232 cells/uL, respectively). An additional 2 patients (1 in each group) met the protocol definition of virologic failure between weeks 48 and 96; no known resistance mutations were observed in the raltegravir recipient; the efavirenz recipient had nucleoside reverse transcriptase inhibitor and nonnucleoside reverse transcriptase inhibitor resistance mutations. Investigator reported drug-related clinical adverse events (AEs) were less frequent with raltegravir (51%) than efavirenz (74%). Drug-related AEs occurring in >10% of patients in either group were nausea in both groups and dizziness and headache in the efavirenz group. Laboratory AEs remained infrequent. Raltegravir had no adverse effect on total or low-density lipoprotein cholesterol or on triglycerides. Neuropsychiatric AEs remained less frequent with raltegravir (34%) than efavirenz (58%). There were no drug-related serious AEs in patients receiving raltegravir.

Conclusions: In antiretroviral therapy–naive patients, raltegravir with TDF/3TC had potent antiretroviral activity, which was similar to efavirenz/TDF/3TC and was sustained to week 96. Raltegravir was generally well tolerated; drug-related AEs were less frequent in patients treated with raltegravir compared with efavirenz.

Key Words: antiretroviral therapy, HIV-1, integrase inhibitor, MK-0518, raltegravir

(*J Acquir Immune Defic Syndr* 2009;52:350–356)

INTRODUCTION

Raltegravir (formerly known as MK-0518) is a strand-transfer inhibitor of HIV-1 integrase[1] that was recently approved for use in combination with other antiretroviral agents in treatment-experienced patients with virologic failure and multidrug-resistant HIV-1 based on potent efficacy and favorable safety data from treatment-experienced patients in Protocol 005[2] and BENCHMRK-1 and -2.[3,4] Potent and durable efficacy of raltegravir sustained to week 48 was also reported in treatment-naive patients enrolled in Protocol 004, a phase II dose-ranging study using raltegravir at 100, 200, 400, or 600 mg twice daily compared with efavirenz, both combined with tenofovir and lamivudine.[5,6] Upon completing week 48 of the dose-ranging phase of the study, patients in Protocol 004 had the option to continue in a double-blind extension phase in which all patients in the raltegravir group received 400 mg twice a day, the dose chosen for further study in the Phase III program and currently the approved dose of raltegravir. This report presents the efficacy and safety data from patients completing at least 96 weeks of therapy in this continuing study of raltegravir 400 mg twice a day in treatment-naive patients with HIV-1 infection.

Received for publication December 9, 2008; accepted January 26, 2009.

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All funding for this study was provided by Merck & Co, Inc.

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METHODS

Study Design

Protocol 004 is a double-blind, randomized, dose-ranging study in treatment-naive HIV-1–infected patients with plasma HIV-1 RNA levels ≥5000 copies per milliliter and $CD4^+$ T-cell counts ≥100 cells per cubic millimeter at screening. Part I consisted of 10 days of raltegravir monotherapy in 35 patients.[6] Part II examined the safety, tolerability, and efficacy of raltegravir dosed 100, 200, 400, or 600 mg twice daily vs efavirenz 600 mg per day, each with tenofovir 300 mg per day and lamivudine 300 mg per day, for up to 48 weeks in 30 patients from part I (cohort I) plus 171 patients randomized into part II (cohort II).[5] Patients who reached week 48 of the original study were given the option to continue in a double-blind extension. Patients who received any dose of raltegravir in the original study received raltegravir 400 mg twice a day in the extension phase. Patients who received efavirenz in the original study continued on efavirenz in the extension. Both open-label drugs, tenofovir and lamivudine, continued unchanged in the extension. This portion of the study (week 48 through week 96) was conducted at 29 sites in the United States, Canada, Latin America, Thailand, and Australia from May 18, 2006 through September 04, 2007. Patients returned to the study sites for physical examinations, laboratory tests, and assessment of virologic and immunologic responses at study weeks 60, 72, 84, and 96.

Patients with lack of response (confirmed plasma HIV-1 RNA >400 copies/mL) or virologic relapse despite compliance with study therapy could be discontinued from study at the discretion of the investigator. Virologic relapse was defined as 2 consecutive measurements (at least 1 week apart) of (1) plasma HIV-1 RNA >400 copies per milliliter after initial response with plasma HIV-1 RNA <400 copies per milliliter or (2) >1.0 $\log_{10}$ increase in plasma HIV-1 RNA above the nadir level. In patients displaying virologic failure (HIV-1 RNA >400 copies/mL at week 24 or early discontinuation or virologic relapse), genotypic and phenotypic resistance assays (Monogram Biosciences, San Francisco, CA) were used to evaluate resistance to tenofovir, lamivudine, and efavirenz at the time of failure as compared with baseline. The emergence of resistance to raltegravir was evaluated by genotyping the integrase coding sequence using methods previously reported.[4]

Statistical Analysis

Antiretroviral Activity

Efficacy analyses were based upon a modified intent-to-treat approach, which included all randomized patients who received at least 1 dose of study medication, regardless of adherence to entry criteria or deviations from the protocol. It was previously reported that all doses of raltegravir showed generally similar efficacy and safety at week 48 in this study[5]; after week 48, all patients on raltegravir received 400 mg twice a day. Therefore, the efficacy data beyond week 48 are displayed in this current analysis as a single raltegravir group that combines all original raltegravir dose groups.

The primary efficacy measurement was the proportion of patients achieving plasma HIV-1 RNA <400 copies per milliliter on the AMPLICOR HIV-1 Monitor Standard assay. Secondary measurements included the proportion of patients achieving plasma HIV-1 RNA <50 copies per milliliter on the UltraSensitive assay, the change from baseline in HIV-1 RNA ($\log_{10}$ copies/mL), and the change from baseline in $CD4^+$ T-cell count. This was an estimation study only and was not powered for formal efficacy comparisons between raltegravir and efavirenz.

For the proportion of patients achieving HIV-1 RNA levels <400 copies per milliliter and <50 copies per milliliter, the noncompleter = failure (NC = F) approach was used; all missing values due to premature discontinuations were considered failures, regardless of the reason for discontinuation and the success/failure status at the time of discontinuation. The difference in proportions between raltegravir and efavirenz groups at 48 and 96 weeks was estimated, and the associated 2-sided confidence interval was derived using Miettinen and Nurminen method.[7] For change from baseline in $CD4^+$ T-cell count and HIV RNA, the observed failure approach was used; baseline value was carried forward for patients who discontinued assigned therapy due to lack of efficacy.

Safety

The safety analysis included all data available through the visit cutoff date of September 04, 2007, including data beyond week 96 in some patients. All patients who took study medication were included in the analysis, which included all adverse events that occurred during study therapy or within 14 days after discontinuation. Laboratory values were examined according to the 1992 Division of AIDS toxicity guidelines for adults (http://rcc.tech-res-intl.com/tox_tables.htm). The differences in proportions of patients with drug-related adverse events (defined as those considered by investigators as possibly, probably, or definitely related to any component of the antiretroviral regimen) were compared using 2-tailed Fisher exact test. To further establish whether raltegravir provides a favorable ratio of benefit to risk in treatment-naive patients, post hoc explorations were performed for neuropsychiatric symptoms and changes in lipid profiles. Since the publication of the week 48 data,[5] it was recognized that 4 terms associated with efavirenz-related central nervous system (CNS) adverse events (dizziness, insomnia, somnolence, and impaired concentration), as noted in the product labeling for efavirenz,[8] were omitted from the original week 48 analysis. For completeness, results described in this article use the expanded list of CNS-related adverse event terms.

Role of the Funding Source

This study was designed by the sponsor (Merck & Co, Inc., Whitehouse Station, NJ) in collaboration with external consultants. The data were collected by the clinical site investigators. The sponsor collated the data, monitored the conduct of the study, performed the statistical analyses, and coordinated the writing of the article with all authors. Data were unblinded for statistical analyses after the databases were locked.

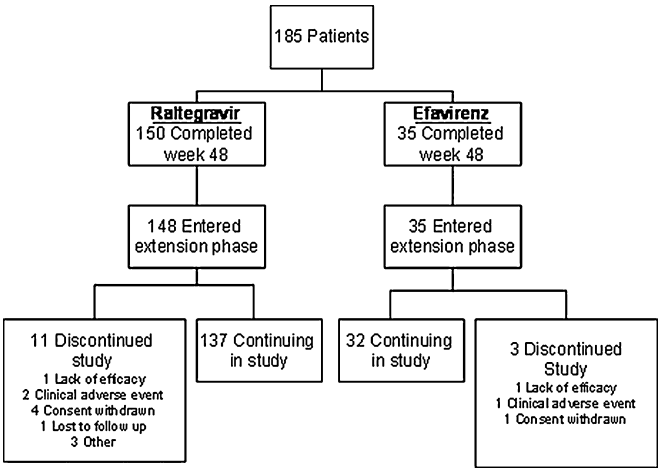

FIGURE 1. Patient disposition through week 96. RAL, raltegravir; EFV, efavirenz; both were given with tenofovir and lamivudine.

RESULTS

Patient Characteristics

A total of 198 patients received study therapy in the original protocol. Baseline characteristics were balanced across treatment groups, as previously described.[5] At baseline, plasma HIV-1 RNA levels were >50,000 copies per milliliter and >100,000 copies per milliliter in 57% and 34% of patients, respectively. The mean HIV-1 RNA level at baseline ranged from 4.6 to 4.8 $\log_{10}$ copies per milliliter. Mean $CD4^+$ T-cell count at baseline ranged from 271 to 338 cells per cubic millimeter. A total of 183 patients entered the extension phase after completing 48 weeks of study therapy. As of September 04, 2007, 169 patients (84%) remained in the study (Fig. 1).

Efficacy

The potent antiretroviral and immunological effect observed in raltegravir-treated patients at week 48 was sustained to week 96 (Table 1). By week 48, all 4 original raltegravir dose groups demonstrated similar efficacy, and these were combined into 1 group for analyses of time points beyond week 48. At week 96, 84% of raltegravir-treated patients and 84% of efavirenz recipients had HIV-1 RNA levels below 400 copies per milliliter (Fig. 2A), with 83% and 84%, respectively, below 50 copies per milliliter (Fig. 2B). The mean change in $CD4^+$ T-cell count from baseline to week 96 was +221 cells per cubic millimeter for raltegravir and +232 cells per cubic millimeter for efavirenz (Fig. 2C). Efficacy endpoints were comparable in patients with baseline HIV-1 RNA levels >100,000 copies per milliliter and ≤100,000 copies per milliliter (Table 2).

Virologic failure occurred in 6 of 160 patients (4%) in the raltegravir group and in 2 of 38 patients (5%) in the efavirenz group by week 96. Most cases of virologic failure occurred before week 48 and have been previously described.[5] One patient in each treatment group developed virologic failure between weeks 48 and 96, and a lack of treatment adherence was suspected based on information collected in medication diaries. Over 96 weeks, treatment-emergent amino acid substitutions in either reverse transcriptase, integrase, or both were identified in 6 of 8 patients with protocol-defined virologic failure. Both patients in whom efavirenz-based therapy failed had mutations conferring resistance to both nucleoside reverse transcriptase inhibitor and nonnucleoside reverse transcriptase inhibitor elements of their regimen. Of the 6 patients with virologic failure during raltegravir-based therapy, 3 had resistance-associated mutations in both the integrase and reverse transcriptase coding regions. The integrase mutations were N155H; L74L/M, V151I, N155H; and Y143C, S230R in the 3 patients. One additional patient who failed raltegravir developed a mutation only in the reverse transcriptase region. Two patients had no resistance-associated mutations in either the integrase or reverse transcriptase coding regions (Table 3).

Safety

Incidence rates for any adverse event, serious adverse events, and discontinuations due to adverse events were

TABLE 1. Summary of Efficacy Endpoints

	Raltegravir		Efavirenz		
	n/N	% (95% CI)	n/N	% (95% CI)	Difference (95% CI)
HIV-1 RNA < 400 copies/mL					
Week 48	148/160	92.5 (87.3 to 96.1)	33/38	86.8 (71.9 to 95.6)	5.7 (−3.4 to 20.3)
Week 96	135/160	84.4 (77.8 to 89.6)	32/38	84.2 (68.7 to 94.0)	0.2 (−10.6 to 15.6)
HIV-1 RNA < 50 copies/mL					
Week 48	137/160	85.6 (79.2 to 90.7)	33/38	86.8 (71.9 to 95.6)	−1.2 (−11.2 to 13.7)
Week 96	133/160	83.1 (76.4 to 88.6)	32/38	84.2 (68.7 to 94.0)	−1.1 (−12.0 to 14.5)
	Baseline mean	Mean change (95% CI)	Baseline mean	Mean change (95% CI)	Difference (95% CI)
Change from baseline in HIV-1 RNA					
Week 48	4.75	−2.32 (−2.43 to −2.22)	4.81	−2.29 (−2.55 to −2.03)	−0.03 (−0.31 to 0.24)
Week 96	4.76	−2.30 (−2.42 to −2.19)	4.82	−2.28 (−2.57 to −2.00)	−0.02 (−0.33 to 0.29)
Change from baseline in $CD4^+$ T-cell count					
Week 48	306	174 (153 to 196)	274	170 (125 to 215)	4 (−45 to 54)
Week 96	298	221 (197 to 246)	277	232 (180 to 285)	−11 (−69 to 47)

CI, confidence interval.

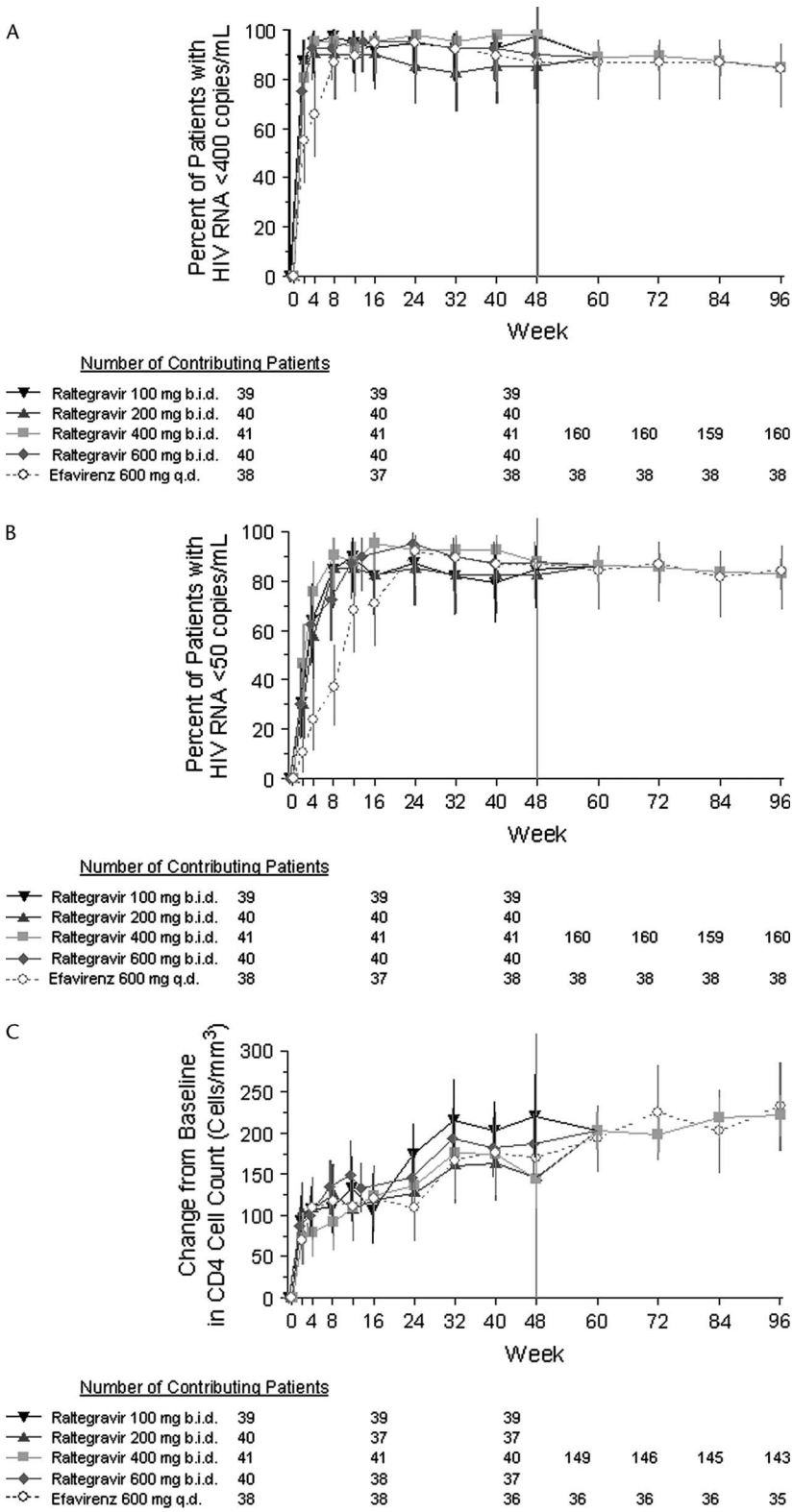

FIGURE 2. Efficacy outcomes through week 96. A, Percent (95% CI) of patients with HIV RNA <400 copies/mL (noncompleter = failure approach). B, Percent (95% CI) of patients with HIV RNA <50 copies/mL (noncompleter = failure approach). C, Mean (95% CI) change from baseline in CD4+ T-cell count (cells/mm^3) (observed failure approach). CI, confidence interval.

similar in patients receiving raltegravir and those receiving efavirenz (Table 4). Drug-related clinical adverse events were reported by fewer patients in the raltegravir group (51%) than in the efavirenz group (74%). Drug-related adverse events with >10% incidence in either treatment group included nausea in patients receiving raltegravir and dizziness, headache, abnormal dreams, nausea, diarrhea, insomnia, and nightmares in patients receiving efavirenz. Neuropsychiatric adverse events

TABLE 2. Efficacy Response* at Week 96 by Baseline HIV-1 RNA Level

	Baseline HIV RNA			
	≤100,000 copies/mL		>100,000 copies/mL	
Treatment	n	Mean (95% CI)	n	Mean (95% CI)
Percent of patients with HIV RNA <400 copies/mL				
Raltegravir 400 mg twice a day	107	84.1 (75.8 to 90.5)	53	84.9 (72.4 to 93.3)
Efavirenz 600 mg every day	24	91.7 (73.0 to 99.0)	14	71.4 (41.9 to 91.6)
Percent of patients with HIV RNA <50 copies/mL				
Raltegravir 400 mg twice a day	107	84.1 (75.8 to 90.5)	53	81.1 (68.0 to 90.6)
Efavirenz 600 mg every day	24	91.7 (73.0 to 99.0)	14	71.4 (41.9 to 91.6)
Change from baseline in HIV RNA (log_{10} copies/mL)				
Raltegravir 400 mg twice a day	94	−2.07 (−2.17 to −1.96)	50	−2.75 (−3.00 to −2.51)
Efavirenz 600 mg every day	23	−2.12 (−2.38 to −1.86)	12	−2.60 (−3.32 to −1.89)
Change from baseline in CD4 cell count (cells/mm^3)				
Raltegravir 400 mg twice a day	93	210 (181 to 240)	50	242 (199 to 284)
Efavirenz 600 mg every day	23	238 (172 to 305)	12	221 (119 to 323)

CI, confidence interval.

*Approach to handling missing values: for percentage of virologic responses, patients who discontinued assigned therapy, regardless of reasons, were considered as failures (noncompleter = failure); For change from baseline in HIV RNA and CD4 cell counts, baseline value was carried forward for patients who discontinued assigned therapy due to lack of efficacy.

(abnormal dreams, depression, nightmares, suicidal ideation, suicide attempt, dizziness, somnolence, adjustment disorder with depressed mood, depressed mood, and insomnia) were less common in the raltegravir group (54 of 160, 34%) than in the efavirenz group (22 of 38, 58%) [95% confidence interval for treatment difference, (−40.3 to −6.7)], primarily due to differences in reports of dizziness (11% vs 34%) and abnormal dreams (7% vs 21%). More than 50% of the neuropsychiatric adverse events were evident by week 8 (data not shown).

In general, few grade 3 or grade 4 laboratory abnormalities were observed through week 96 (Table 5). Creatine phosphokinase (CPK) elevations meeting Division of AIDS grade 3 or grade 4 criteria were observed in 6.3% (10 patients) and 2.6% (1 patient) in the raltegravir and efavirenz groups, respectively, over the 96-week study. Of the 10 cases in the raltegravir group, 3 occurred after week 48, and overall, 6 of the 10 were considered related to strenuous exercise. No cases were associated with clinical adverse experiences such as myopathy, myositis, or rhabdomyolysis, and none required

TABLE 3. Treatment Emergent Mutations in Patients With Virologic Failure

		Treatment Emergent Mutations			
Treatment Group	Virologic Failure Type	Raltegravir	Lamivudine	Tenofovir	Efavirenz
Raltegravir	Nonresponse*†	L74L/M,V151I, N155H	M184M/I/V, K65K/R	K65K/R	—
	Relapse‡	Y143C, S230R§	M184M/I/V	—	—
	Relapse‖	—	—	—	—
	Non-response*	N155H	M184M/I/V	—	—
	Non-response*	—	M184V	—	—
	Relapse¶#	—	—	—	—
Efavirenz	Non-response*	—	K65R	K65R	G190E
	Relapse¶**	—	M184V	—	Y188L, K103K/N

Protocol definition of virologic failure: (1) nonresponse: >400 copies/mL at week 24 or early discontinuation, (2) virologic relapse: >400 copies/mL after initial response of <400 copies/mL, or >1.0 log_{10} increase above nadir level. Mutations are shown for viruses isolated after virologic failure or relapse. Data from the most recent time point tested are shown. For MK-0518, confirmed resistance mutations are shown for those residues present in the virus isolated at failure but not in the baseline isolate. For lamivudine, tenofovir, and efavirenz, mutations shown are those determined by Monogram Biosciences to be associated with resistance.

Note: "—" indicates no confirmed resistance mutations.

*All 4 patients with nonresponse achieved >1.0 log_{10} decrease in HIV RNA at the nadir.

†Patient also has I135I/V, K156K/R, I208M, and D232N integrase mutations at postfailure time point. At an earlier failure time point, patient had V151I, N155H, G163G/R, and D232N/D integrase mutations.

‡Patient also has E48E/K, V75V/M, T124T/N, I135V, and S255N integrase mutations at postfailure time point. This patient had the V151I polymorphism before protocol entry and throughout therapy.

§Mutations developed after virologic failure.

‖Patient also has T174T/A, I182T/I integrase mutations at postfailure time point.

¶After being virally suppressed (by protocol definition) for 48 weeks.

#Patient also has H16H/Y, A21A/T, C56C/W, Y83Y/S, D232D/N, L242L/F, and V260V/G,R262R/K integrase mutations at postfailure time point.

**Patient also has H183H/P, M275M/V integrase mutations at postfailure time point.

TABLE 4. Summary of Adverse Events

	Raltegravir, 400 mg Twice a Day, (N = 160) n (%)	Efavirenz, 600 mg Every Day, (N = 38) n (%)
One or more clinical adverse events	146 (91.3)	35 (92.1)
Serious clinical adverse events	16 (10.0)	3 (7.9)
Discontinued due to clinical adverse event	2 (1.3)	1 (2.6)
Drug-related* clinical adverse events†	82 (51.3)	28 (73.7)
Diarrhea	11 (6.9)	4 (10.5)
Nausea	20 (12.5)	5 (13.2)
Vomiting	4 (2.5)	3 (7.9)
Flatulence	9 (5.6)	1 (2.6)
Dizziness	14 (8.8)	11 (28.9)
Headache	14 (8.8)	9 (23.7)
Abnormal dreams	10 (6.3)	7 (18.4)
Insomnia	13 (8.1)	4 (10.5)
Nightmares	0 (0.0)	4 (10.5)
Fatigue	8 (5.0)	2 (5.3)
Malaise	2 (1.3)	3 (7.9)
Anxiety	2 (1.3)	2 (5.3)
Lethargy	2 (1.3)	2 (5.3)
Disturbance in attention	1 (0.6)	2 (5.3)
One or more laboratory adverse events	38 (23.8)	11 (28.9)
Discontinued due to laboratory adverse event	1 (0.6)	0 (0.0)
Drug-related* laboratory adverse events†	19 (11.9)	3 (7.9)
Aspartate aminotransferase increased	7 (4.4)	2 (5.3)
Alanine aminotransferase increased	6 (3.8)	2 (5.3)

*Determined by investigator to be possibly, probably, or definitely related to any drug in the study regimen.

†Specific events occurring in at least 5% of patients in 1 or more treatment groups are listed.

permanent discontinuation of study therapy. Raltegravir was temporarily interrupted due to a grade 4 CPK elevation in 1 patient and did not recur with rechallenge. In all cases, grade 3 or grade 4 CPK elevations were brief in duration and resolved.

TABLE 5. Grade 3/4† Abnormalities for Prespecified Laboratory Tests

Laboratory Tests	Toxicity Criteria*	Raltegravir (N = 160) n (%)	Efavirenz (N = 38) n (%)
Absolute neutrophil count	<750 cells/μL	1 (0.6)	0 (0.0)
Fasting LDL cholesterol	≥190 mg/dL	1 (0.6)	2 (5.3)
Fasting total cholesterol	>300 mg/dL	0 (0.0)	2 (5.3)
Fasting triglycerides	>750 mg/dL	0 (0.0)	3 (7.9)
Alkaline phosphatase	>5 × ULN	1 (0.6)	0 (0.0)
Pancreatic amylase	>2 × ULN	4 (2.5)	0 (0.0)
Lipase	>3 × ULN	2 (1.3)	0 (0.0)
Aspartate aminotransferase	>5 × ULN	4 (2.5)	1 (2.6)
Alanine aminotransferase	>5 × ULN	2 (1.3)	2 (5.3)
Creatine kinase	≥10 × ULN	10 (6.3)	1 (2.6)

No grade 3 or 4 abnormalities were reported in either treatment group for the following parameters: hemoglobin, platelet count, fasting glucose, creatinine, and total bilirubin.

*Grades 3/4 by DAIDS criteria [http://rcc.tech-res-intl.com/tox_tables.htm].

DAIDS, Division of AIDS; LDL, low-density lipoprotein; ULN, upper limit of normal.

Detailed analyses of serum lipid profiles were performed at baseline and at intervals including at week 96 (Table 6). No clinically relevant elevation of triglycerides, total cholesterol, or low-density lipoprotein cholesterol was observed in the raltegravir group compared with the efavirenz group. At week 96, the mean change in the ratio of total to HDL cholesterol was −0.74 (from 4.58 at baseline) in the raltegravir group and −0.66 (from 4.57 at baseline) in the efavirenz group. In this study population, a prior diagnosis of hyperlipidemias (such as dyslipidemia, hypercholesterolemia, hyperlipidemia, or hypertriglyceridemia) was uncommon, occurring in 4.4% of the raltegravir group and 5.3% of the efavirenz group. Similarly, the initiation of treatment with any lipid-lowering agents (including prescription medications and nutritional supplements such as omega 3 fatty acids), while the patient was on study therapy, was relatively infrequent and similar in both groups (4.4% in the raltegravir group and 7.9% in the efavirenz group). Similarly, the initiation of lipid-lowering prescription medications (defined as statins, fibrates, ezetimibe, and cholestyramine) occurred in 2.5% and 5.3% of the raltegravir and efavirenz groups, respectively. Reports of hyperlipidemias occurring as adverse events were also infrequent; increased blood triglycerides occurred in 1.3% and 5.3% of the raltegravir and efavirenz treatment groups, respectively, and increased low-density lipoprotein cholesterol occurred in 1 patient in the raltegravir group (0.6%) and in no patients in the efavirenz group.

DISCUSSION

The treatment paradigm for HIV-1 infection continues to evolve. Currently, the use of antiretroviral agent combinations

TABLE 6. Mean Change from Baseline in Serum Lipids

	Raltegravir		Efavirenz		RAL vs EFV
	Baseline Mean	Mean Change*	Baseline Mean	Mean Change*	Nominal *P* Value†
Total cholesterol (mg/dL)					
Week 48	165.9	−2.3	168.7	+20.7	<0.001
Week 96	166.2	+1.1	168.9	+24.0	0.002
LDL-C (mg/dL)					
Week 48	103.8	−7.5	108.9	+3.0	0.016
Week 96	103.9	−5.8	108.5	+4.4	0.045
HDL-C (mg/dL)					
Week 48	37.8	+4.8	36.7	+9.8	0.010
Week 96	38.0	+7.4	37.9	+13.0	0.017
Triglycerides (mg/dL)					
Week 48	131.8	−1.0	127.3	+49.5	0.068
Week 96	134.7	−10.8	126.1	+13.4	0.145
Total: HDL ratio					
Week 48	4.6	−0.6	4.7	−0.5	0.530
Week 96	4.6	−0.7	4.6	−0.7	0.689

*Mean change from baseline was based on the measurements of the patients who were measured at baseline and the time point assessed.

†Nominal *P* value was calculated from *t* test.

LDL-C, low-density lipoprotein cholesterol; EFV, efavirenz; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; RAL, raltegravir.

can achieve sustained control of viral replication and improved immune function in the majority of treatment-naive and treatment-experienced patients. Among the newest agents, raltegravir, a strand-transfer inhibitor of the HIV-1 integrase enzyme, dosed at 400 mg twice daily without regard to food, has been approved for use in treatment-experienced patients who have evidence of ongoing viral replication and multidrug resistance. This approval is based largely on the results of the BENCHMRK trials,[3,4] where raltegravir proved superior to placebo when added to an optimized background regimen. After 48 weeks of treatment in Protocol 004, potent efficacy and favorable tolerability and safety of raltegravir in treatment-naive patients were also reported.[5] This report confirms that a continued and durable suppression of viral replication, comparable to that obtained with an efavirenz-based regimen, is achieved with raltegravir-based therapy at the 400 mg twice a day dose, both with 2 nucleoside reverse transcriptase inhibitors, through 96 weeks, after the initial 48 weeks of raltegravir dosed at 100–600 mg twice daily. In addition, the raltegravir regimen maintained a favorable adverse event profile in treatment-naive HIV-1–infected patients. These results are consistent with the results of a large Phase III study of raltegravir compared with efavirenz in combination with a fixed-dose combination of tenofovir and emtricitabine in treatment-naive patients demonstrating noninferiority of the raltegravir-containing regimen.[9]

The durability of the antiretroviral response of raltegravir for at least 96 weeks observed in this study is noteworthy. That 83% of 160 treated patients maintained plasma HIV-1 levels below the 50-copy detection limit suggests that the raltegravir-based combination therapy is comparable in activity and durability to an efavirenz-based combination regimen.[10,11] This will be confirmed in the larger, ongoing Phase III study noted above. Interestingly, in the current study, only 1 patient in each treatment group had virologic failure beyond week 48. Both of these patients had a suspected lack of treatment compliance, and the patient in the raltegravir group had no evidence of any integrase-associated resistance mutations.

The 96-week safety and tolerability results continue to demonstrate the lipid neutrality of raltegravir-based therapy. Furthermore, there seems to be a distinction between the 2 treatment arms regarding neuropsychiatric adverse events, which if confirmed in larger studies, may be important in future treatment decisions for treatment-naive patients. The imbalance in the incidence of grade 3 or grade 4 CPK elevations between the treatment groups confirms previously reported data from the BENCHMRK studies[3] that raltegravir therapy may be associated with asymptomatic elevation in CPK levels. In postmarketing reports, rhabdomyolysis has been reported in patients receiving raltegravir and concomitant therapy with statins[12] and should therefore be used with care in patients predisposed to rhabdomyolysis, that is, patients on concomitant therapy with statins.

In summary, in this Phase II study, raltegravir 400 mg twice daily in combination with 2 nucleoside reverse transcriptase inhibitors has demonstrated potent durable efficacy similar to that of an efavirenz-based regimen and has been generally well tolerated. Results of an ongoing Phase III study of raltegravir in treatment-naive subjects are expected to provide more information on the potential role of a raltegravir-based treatment regimen for the HIV-1–infected, treatment-naive patient.

ACKNOWLEDGMENTS

The authors would like to thank the patients for their participation in this study and the other members of the Protocol 004 Study Team for their contributions. They would also like to thank Neal Azrolan and Karyn Davis (Medical Communications, Merck Research Laboratories, North Wales, PA) for their assistance with the article.

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APPENDIX 1: PROTOCOL 004 STUDY TEAM

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