Long-term Treatment With Raltegravir *or* Efavirenz Combined With Tenofovir/Emtricitabine for Treatment-Naive Human Immunodeficiency Virus-1–Infected Patients: 156-Week Results From STARTMRK

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Background. We compared 3 years of antiretroviral therapy with raltegravir or efavirenz as part of a combination regimen in the ongoing STARTMRK study of treatment-naive patients infected with human immunodeficiency virus (HIV).

Methods. Eligible patients with HIV-1 RNA (vRNA) levels >5000 copies/mL and without baseline resistance to efavirenz, tenofovir, or emtricitabine were randomized in a double-blind, noninferiority study to receive raltegravir or efavirenz, each combined with tenofovir/emtricitabine. Outcomes included viral suppression, adverse events, and changes from baseline metabolic parameters. Dual energy X-ray absorptiometry scans were obtained on a convenience sample of patients at prespecified time points to assess changes in body fat composition.

Results. At week 156 counting noncompleters as failures, 212 (75.4%) of 281 versus 192 (68.1%) of 282 had vRNA levels <50 copies/mL in the raltegravir and efavirenz groups, respectively [Δ (95% CI) = 7.3% (−0.2, 14.7), noninferiority $P < .001$]. Mean changes from baseline CD4 count were 332 and 295 cells/mm^3 in the raltegravir and efavirenz arms, respectively [Δ (95% CI) = 37 (4, 69)]. Consistent virologic and immunologic efficacy was maintained across prespecified demographic and baseline prognostic subgroups for both treatment groups. Fewer drug-related clinical adverse events (49% vs 80%; $P < .001$) occurred in raltegravir than efavirenz recipients, with discontinuations due to adverse events in 5% and 7%, respectively. Elevations in fasting lipid levels (including LDL- and HDL-cholesterol) were consistently lower in the raltegravir than efavirenz group ($P < .005$). Fat gain was 19% in 25 raltegravir recipients and 31% in 32 efavirenz recipients at week 156.

Conclusions. When combined with tenofovir/emtricitabine in treatment-naive patients, raltegravir produced durable viral suppression and immune restoration that was at least equivalent to efavirenz through 156 weeks of therapy. Both regimens were well tolerated, but raltegravir was associated with fewer drug-related clinical adverse events and smaller elevations in lipid levels.

Clinical Trials Registration. NCT00369941

Raltegravir as part of combination antiretroviral therapy has proven efficacious and generally well tolerated in patients infected with human immunodeficiency virus type 1 (HIV-1) susceptible or resistant to other classes of antiretroviral drugs [1–5]. In the Phase III STARTMRK study of treatment-naive patients, the efficacy of raltegravir was noninferior to the results with efavirenz when used in combination with tenofovir/emtricitabine

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through 96 weeks of therapy [4, 5]. Raltegravir recipients experienced fewer clinical adverse events than efavirenz recipients. As HIV treatment has evolved to a paradigm of lifelong therapy for many patients, often with comorbid conditions, long-term efficacy and safety data are essential to distinguish among antiretroviral regimens. Accordingly, we analyzed the 156-week results from STARTMRK, with particular attention to metabolic parameters including changes in lipid profiles and body fat composition.

METHODS

Study Design

STARTMRK (MK-0518 protocol 021) is an ongoing blinded, randomized, active-controlled Phase III clinical trial enrolling patients from 67 sites on 5 continents [4, 5]. The protocol was approved by the Institutional Review Boards or Ethical Review Committees at each site and conducted in accordance with Good Clinical Practice guidelines. All participants provided written informed consent. The primary analysis was performed at week 48 as specified in the protocol. The trial was monitored by an independent Data and Safety Monitoring Board until 4 August 2009 after review of complete 96-week data when the committee disbanded itself. Continued double-blind follow-up is planned for a total duration of 5 years.

As described in detail elsewhere [4], treatment-naive HIV-infected patients ≥18 years of age were eligible if their vRNA levels were >5000 copies/mL without genotypic resistance to tenofovir, emtricitabine, and/or efavirenz. Patients were stratified by baseline vRNA levels (>50 000 vs ≤50 000 copies/mL) and viral hepatitis coinfection status, defined by hepatitis B surface antigen positivity and/or detection of hepatitis C RNA by polymerase chain reaction (see Supplementary Appendix for Expanded Methods; online only). After stratification, patients were randomly assigned in a 1:1 ratio to receive raltegravir or efavirenz, each in combination with coformulated tenofovir and emtricitabine. Participants were instructed to take tenofovir 300 mg and emtricitabine 200 mg coformulated as a single tablet (Truvada) in the morning with food, a 400-mg tablet of raltegravir or matching placebo twice daily at approximately 12-hour intervals without regard to food intake, and a 600-mg tablet of efavirenz or identical placebo on an empty stomach at the hour of sleep.

Procedures

HIV RNA levels were measured at a central laboratory using the standard COBAS Amplicor HIV-1 Monitor assay (version 1.5; Roche Diagnostics) with a lower limit of quantification of 400 vRNA copies/mL and the Ultrasensitive Amplicor HIV-1 Monitor assay (version 1.5; Roche Diagnostics) with a lower quantification limit of 50 vRNA copies/mL. To measure changes in body fat composition over time on study drugs, dual energy X-ray absorptiometry (DEXA) scans were to be obtained on a subset of patients from sites in the United States that had access to the necessary equipment at the baseline, week-48, week-96, and week-156 visits. All DEXA scans were submitted to a central reader (Synarc) for interpretation.

Statistical Analyses

All randomized and treated patients were included in the efficacy and safety analyses. This report presents efficacy results through week 156 and all available safety data through 13 July 2010 (the date when the last patient remaining in the study completed the week-156 visit). Primary and secondary analyses were specified at weeks 48 and 96, respectively, per protocol. Standard outcomes were also analyzed at week 156, for which nominal *P* values and 95% confidence intervals (CI) were computed. Analyses of the nervous system adverse events and DEXA results were based on 156-week data. Fasting blood samples were scheduled to be obtained at the week-144 visit and compared with fasting baseline values.

Similarly to the prespecified analyses, after adjustment for stratification of baseline vRNA concentration, raltegravir would be judged noninferior to efavirenz if the lower bound of the 2-sided 95% CI for the proportion of patients who responded in the raltegravir group minus the efavirenz group at week 156 was higher than the prespecified noninferiority margin of −12%, using the method of Miettinen and Nurminen [6]. For calculation of virologic response rates, the primary approach to handling missing data was to include all noncompleters as failures (NC=F). Two additional prespecified approaches for handling missing data (treatment-related discontinuation [TRD]=F and observed failure [OF]) were performed as sensitivity analyses for the efficacy outcomes [7]. In the TRD=F analysis of virologic response rates, only treatment-related discontinuations were considered as failures without imputation of data for other drop-outs. An OF approach, which allowed evaluation of efficacy without confounding by discontinuations due to intolerability or other non–treatment-related reasons, was used for assessing changes from baseline CD4-cell counts and for the prespecified subgroup analyses based on demographic and prognostic factors at baseline.

Adverse events occurring during the double-blind phase of the study or within 14 days after discontinuation were included in this analysis. Adverse-event terms were adapted from the Medical Dictionary for Regulatory Activities (MedDRA version 13.0). Adverse events were considered to be drug-related if judged by the investigator as definitely, probably, or possibly related to any of the study drugs. The intensity of clinical adverse events was graded by the investigator as mild, moderate, or severe. Severity of laboratory abnormalities was graded according to the 1992 DAIDS toxicity guidelines for adults.

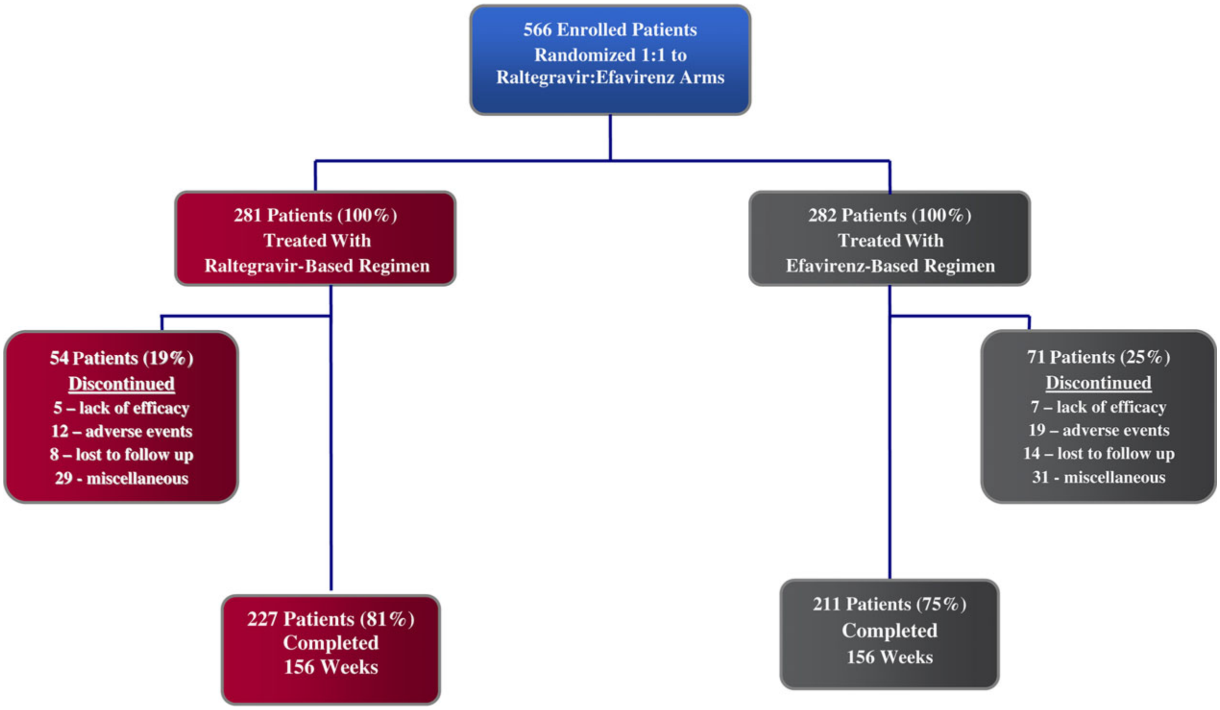

Figure 1. A CONSORT diagram shows patient disposition through study week 156. A total of 3 randomized patients, including 1 patient in the raltegravir arm and 2 patients in the efavirenz arm, never received study drugs. For the calculation of percentages subsequent to entry, the number of treated patients in each group was assigned a value of 100%. At the time the last remaining patient completed the week-156 visit, 2 additional raltegravir recipients (including 1 for an adverse event) and 7 additional efavirenz recipients (including 2 for an adverse event and 2 lost to follow-up) had discontinued the study.

For analysis of fasting lipid and glucose levels scheduled at the week-144 visit, missing data were handled by carrying the last observation forward. If patients had initiated or increased the dosage of lipid-lowering therapy, the last available lipid value prior to the medication change was used in the analysis. No missing data were imputed for the 2 analyses of body composition measurements by DEXA, based either on all available scans at each time point or only on scans available at both baseline and week 156.

RESULTS

Baseline Characteristic and Patient Accounting

Baseline characteristics are described for all treated patients, as well as for the convenience sample of 57 patients with DEXA scans at both baseline and week 156 in Supplementary Table S1. Subject disposition through week 156 is presented in Figure 1. Prior to week 96, 36 patients (13%) in the raltegravir group and 50 patients (18%) in the efavirenz group discontinued the study. An additional 18 raltegravir recipients and 21 efavirenz recipients discontinued between week 96 and week 156, including 0 and 2 patients due to lack of efficacy, 2 and 3 patients because of adverse events, and 5 and 6 patients who did not enter the study extension at week 96 in the respective raltegravir and efavirenz groups. Subsequent to their week-156 visit but before the cutoff date for the present analysis, 2 more raltegravir recipients and 7 more efavirenz recipients left the study. At the cutoff date, the median [range] time on study was 171 [8, 200] and 167 [2, 199] weeks for the respective raltegravir and efavirenz groups, accounting for 830 and 788 person-years of treatment overall.

Virologic and Immunologic Responses

In the NC=F analysis at week 156, 212 (75.4%) of 281 raltegravir recipients and 192 (68.1%) of 282 efavirenz recipients achieved vRNA levels <50 copies/mL (Table 1), compared with 86% and 82% at primary week-48 time point, respectively (Figure 2*A*). The week-156 treatment difference (Δ [95% CI]) of 7.3% [−0.2, 14.7] was consistent with the efficacy of raltegravir being noninferior to efavirenz through 156 weeks ($P < .001$). Counting only treatment-related discontinuations as failures, response rates at week 156 were 85% for raltegravir recipients and 77% for efavirenz recipients, with a treatment difference of 8 [1,15]. Viral suppression <400 vRNA copies/mL was more often achieved at week 156 in the raltegravir than in the efavirenz group.

Using an observed-failure approach for exploratory subgroup analyses at week 156, consistent virologic and immunologic effects were maintained across key demographic and baseline prognostic factors, including gender, age, race, vRNA level (≤ vs >100 000 copies/mL), CD4 count (≤ vs >200 cells/mm^3), HIV-1 subtype (B vs non-B clades), and hepatitis B and/or C coinfection for both treatment groups at week 156 (Table 2). A post hoc analysis of virologic response rates broken down by baseline vRNA levels ≤50 000, >50 000 to ≤100 000, >100 000 to ≤250 000, and >250 000 copies/mL for each treatment group is presented in Supplementary Table S2. Mean [95% CI] changes in CD4 counts from baseline to week 156 were 332 [309, 354] cells/mm^3 for raltegravir recipients and 295 [271, 319] cells/mm^3 for efavirenz recipients (Δ [95% CI] = 37 [4, 69] cells/mm^3). CD4-cell counts continued to rise after week 96 in both groups (Figure 2*B*).

Safety and Tolerability

Almost all patients experienced at least 1 clinical adverse event (Table 3), leading to discontinuations in 5% of the raltegravir group and 7% of the efavirenz group. The types and frequencies of all serious adverse events irrespective of causality reported through the cutoff date for this analysis are presented in Supplementary Table S3. The incidence of serious adverse events was 17% in each treatment group. New serious clinical adverse events were reported in 11 raltegravir recipients and 17 efavirenz recipients between week 96 and week 156. Fewer drug-related clinical adverse events (50% vs 80%; $P < .001$) occurred with raltegravir than with efavirenz recipients. The cumulative frequencies of specific drug-related clinical adverse events of moderate or severe intensity occurring in ≥2% of either treatment group are listed in Table 4. Laboratory adverse events were reported in a minority of patients in both groups. Grades 3/4 laboratory abnormalities are listed in Table 5.

New or recurrent cancers were reported in 5 raltegravir and 12 efavirenz recipients overall, with 3 and 2 cases in each treatment arm, respectively, diagnosed after 96 weeks. No immune reconstitution syndromes were reported as serious adverse events after 96 weeks. There were 4 deaths during the study in the raltegravir group; the causes of death were reported as Kaposi's sarcoma at week 8, cerebral hemorrhage at week 13, metastatic lung cancer at week 91, and recreational drug and alcohol toxicity at week 123. One additional death occurred in an efavirenz recipient from sepsis at week 126. No death was judged to be drug-related.

The cumulative frequencies of treatment-emergent abnormalities of fasting lipid levels up until the cutoff date are displayed in Supplementary Table S4. Mean changes from baseline in fasting total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglyceride levels were significantly smaller in raltegravir than efavirenz recipients at week 144 (Figure 3). There was a trend toward a greater decrease from baseline in the total cholesterol:HDL-cholesterol ratio for raltegravir (−0.20) than efavirenz (+0.04) recipients ($P = .06$). Lipid-lowering medication was a concomitant treatment in 5% of subjects in the raltegravir group and 3% of subjects in the efavirenz group at entry, and in 9% of subjects in the raltegravir group and 10% of

Table 1. Virologic Response Rates at Week 156

Different approaches to missing data	Proportion of patients with vRNA level <50 copies/mL				Proportion of patients with vRNA level <400 copies/mL			
	Raltegravir group, n/m (%)	Efavirenz group, n/m (%)	Between-group difference (95% CI[a])	Noninferiority *P* value	Raltegravir group, n/m (%)	Efavirenz group, n/m (%)	Between-group difference (95% CI[a])	Noninferiority *P* value
Noncompleter = failure (NC=F)	212/281 (75.4)	192/282 (68.1)	7.3 (−0.2, 14.7)	<.001	224/281 (79.7)	203/282 (72.0)	7.6 (0.5, 14.6)	<.001
Treatment-related discontinuation = failure (TRD=F)	212/249 (85.1)	192/249 (77.1)	8.0 (1.2, 14.9)	<.001	224/249 (90.0)	203/249 (81.5)	8.5 (2.4, 14.7)	<.001
Observed failure (OF)	212/237 (89.5)	192/227 (84.6)	4.9 (−1.3, 11.1)	<.001	224/237 (94.5)	203/227 (89.4)	5.2 (0.2, 10.5)	<.001

Abbreviations: CI, confidence interval; n/m, number of patients with the indicated vRNA level / number of patients eligible for the specified analysis.

[a] The 95% CIs and *P* values for treatment differences were calculated using the method of Miettinen and Nurminen [6] with weights proportional to the size of each stratum (screen HIV RNA >50 000 copies/mL or ≤50 000 copies/mL). A 95% CI for the difference excluding a decrease of ≥12% and associated 1-sided *P* value ≤.025 implies that the difference is statistically significantly less than the prespecified clinically relevant decrease of 12% and allows for a conclusion of noninferiority.

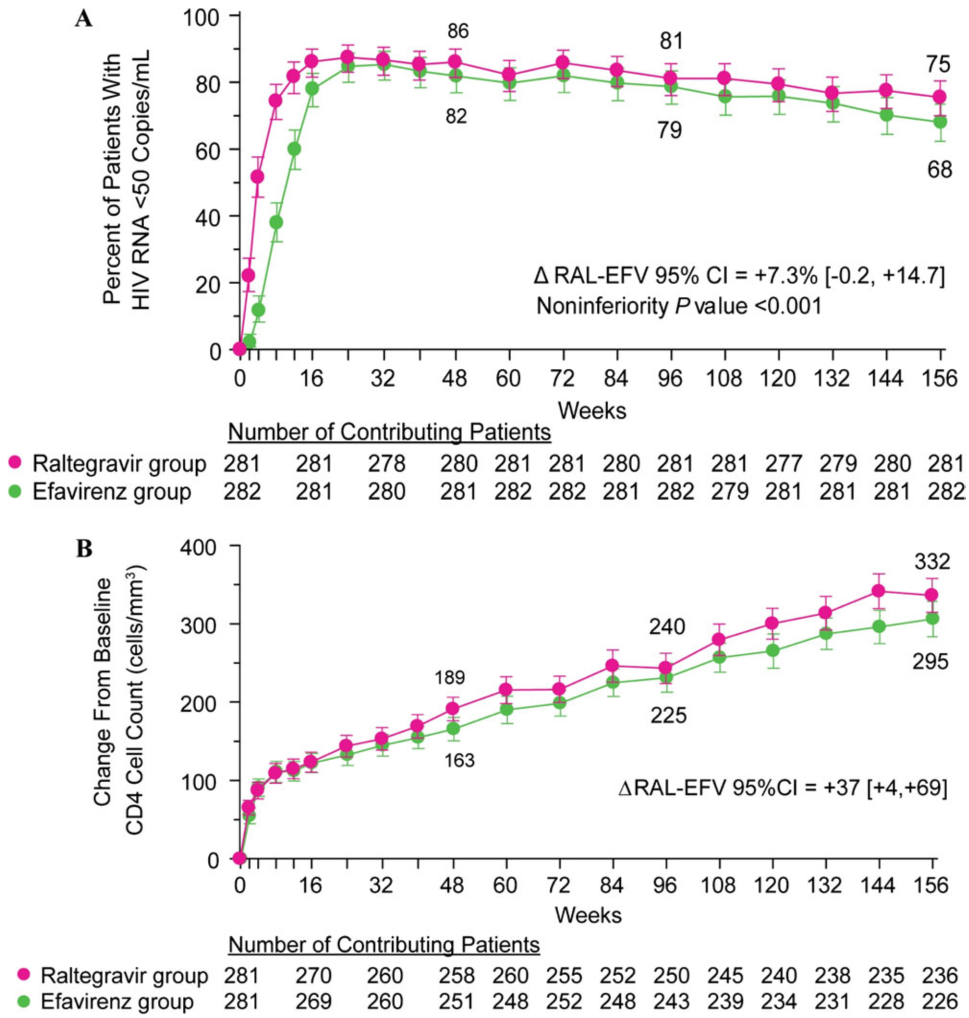

Figure 2. Time course of virologic response rates (confirmed vRNA level <50 copies/mL) (*A*) and CD4-cell count increments (*B*) by treatment group. Missing data were handled by NC=F approach for virologic responses and by an observed-failure approach for CD4 counts.

subjects in the efavirenz group at some point through week 144. Mean changes in fasting glucose levels between baseline and week 144 were small in both groups.

Body mass index increased in both treatment groups (Figure 4). Concurrently, DEXA scans obtained on a convenience sample of 57 patients at both baseline and week 156 revealed a mean overall fat gain for trunk plus limbs of 19% in the raltegravir versus 31% in the efavirenz group. Similar temporal trends were found when all patients with DEXA scans at any time point were included in the analysis (Supplementary Figure S1). The majority of patients in both treatment groups gained modestly more central fat than limb fat. Lipoatrophy (defined as loss of ≥20% appendicular fat) occurred in 1 (4%) of 25 raltegravir recipients and 2 (6%) of 32 efavirenz recipients by week 156. There was no discordance between appendicular and trunk fat loss for these few patients. None of the patients with lipoatrophy identified by DEXA scanning had investigator-reported lipodystrophy as an adverse event.

Virologic Failure and Antiretroviral Drug Resistance

Cumulatively, 104 patients experienced virologic failure by week 156, including 19/50 raltegravir recipients and 16/54 efavirenz recipients with vRNA levels >400 copies/mL which were sent for resistance testing. Raltegravir-resistant virus was demonstrated in 4 of the 19 patients in the raltegravir group (1 case each showing Q148H + G140S, Q148R + G140S, Y143H + L74L/M + E92Q + T97A, Y143R); in 3 of these 4 cases, the viruses were also emtricitabine-resistant but sensitive to tenofovir. In 3 additional cases, only emtricitabine resistance was detected. Efavirenz-resistant virus was demonstrated in 7 of the 16 patients in the efavirenz group (all had the K103N mutation, with K103N alone in 3 cases); in 3 of these 7 cases, the viruses were also emtricitabine-resistant but sensitive to tenofovir. In 2 additional cases, only emtricitabine resistance was detected.

Between weeks 96 and 156, 20 patients (11 in the raltegravir group and 9 in the efavirenz group) met the protocol definition of virologic failure, 8 of whom (3 raltegravir recipients and 5

Table 2. Exploratory Subgroup Analysis of Week 156 Treatment Effect Across Prespecified Baseline Factors

Baseline variable	Virologic response rates (vRNA <50 copies/mL) by observed-failure approach at week 156: Raltegravir group n/N (%)	Efavirenz group n/N (%)	Percent difference [95% CI] in response rates
Overall	212/237 (89)	192/227 (85)	5 [−1, 11]
Gender			
Female	40/43 (93)	33/39 (85)	8 [−6, 24]
Male	172/194 (89)	159/188 (85)	4 [−3, 11]
Age (years)			
≤37	109/124 (88)	108/131 (82)	5 [−3, 14]
>37	103/113 (91)	84/96 (88)	4 [−5, 13]
Race/Ethnicity[a]			
Black	18/23 (78)	17/22 (77)	1 [−24, 26]
White	83/94 (88)	82/90 (91)	−3 [−12,6]
Hispanic	50/54 (93)	42/55 (76)	16 [3, 30]
Asian	31/34 (91)	23/27 (85)	6 [−11, 25]
Native American	1/1 (100)	…	…
Multiracial	29/31 (94)	28/33 (85)	9 [−8, 26]
Plasma vRNA level (copies/mL)			
≤100 000	99/105 (94)	93/111 (84)	11 [2, 19]
>100 000	113/132 (86)	99/116 (85)	0 [−9, 9]
CD4 count (cells/mm^3)			
≤50	16/23 (70)	24/28 (86)	−16 [−39,7]
>50 to ≤200	80/89 (90)	68/84 (81)	9 [−2, 20]
>200	116/125 (93)	100/115 (87)	6 [−2, 14]
HIV-1 subtype[b]			
Clade B	162/184 (88)	154/182 (85)	3 [−4, 11]
Non–clade B	47/50 (94)	34/40 (85)	9 [−4, 24]
Hepatitis coinfection			
B and/or C	11/12 (92)	11/13 (85)	7 [−24, 37]
Neither B or C	201/225 (89)	181/214 (85)	5 [−2, 11]

Abbreviations: n, the number of responders in the specified subgroup; N, the total number of treated patients evaluable at week 156 in the specified subgroup using an observed-failure approach; CI, confidence interval.

[a] Self-reported.

[b] The viral subtype was missing in 3 raltegravir recipients and 5 efavirenz recipients.

efavirenz recipients) had vRNA levels >400 copies/mL. Virus from only 1 of the 3 evaluable raltegravir recipients had any detectable resistance, which was confined to emtricitabine; no new resistance to raltegravir was detected by standard bulk population sequencing subsequent to week 48. Virus from 4 of 5 evaluable efavirenz recipients had detectable resistance to drugs in their regimen: 1 had virus resistant only to efavirenz, 2 had virus resistant only to emtricitabine; and 1 had virus resistant to efavirenz, tenofovir, and emtricitabine.

DISCUSSION

The extended STARTMRK results demonstrate that raltegravir combined with tenofovir/emtricitabine exerted a durable antiretroviral effect in treatment-naive patients through 156 weeks. The virologic response rate with the raltegravir regimen remained statistically noninferior to (and numerically higher than) the response rate with the control efavirenz regimen at week 156. The mean increment in week-156 CD4 cell counts from baseline was modestly higher with raltegravir than efavirenz therapy. Raltegravir recipients experienced significantly fewer drug-related clinical adverse events (and numerically less clinical adverse events overall) than efavirenz recipients. Serious adverse events and discontinuations due to adverse events developed with comparable frequency in both treatment groups. Relatively few patients in either group who had not experienced serious adverse events during the first 96 weeks of the study developed such adverse effects later. No late-appearing immune reconstitution syndromes were reported in either treatment group. Cancers were diagnosed less often in raltegravir-treated patients than in the control group. Although judged to be unrelated to study medication, 4 of the 5 deaths

Table 3. Types and Frequencies of Adverse Events (AE)

	Clinical adverse events				Laboratory adverse events			
No. of participants	Raltegravir group N = 281	Efavirenz group N = 282	Δ%[a] (95% CI)	P[b]	Raltegravir group N = 281	Efavirenz group N = 281	Δ%[a] (95% CI)	P[b]
With one or more AE	268 (95)	276 (98)	−3 (−6, 0.5)	.109	45 (16)	64 (23)	−7 (−13, −0.2)	.006
With drug-related AE[c]	140 (50)	225 (80)	−30 (−37, −22)	<.001	23 (8)	33 (12)	−4 (−9, 1.5)	.205
With serious AE[d]	47 (17)	47 (17)	0 (−6, 6)	1.000	0 (0)	2 (1)	−1 (−3, 1)	.499
With serious drug-related AE[c]	6 (2)	6 (2)	0 (−3, 3)	1.000	0 (0)	1 (0.4)	−0.4 (−2, 1)	1.000
Who dscontinued due to AE[e]	13 (5)	21 (7)	−3 (−7, 1)	.215	0 (0)	3 (1)	−1 (−3, 0.3)	.249
Who discontinued due to drug-related AE[c]	3 (1)	14 (5)	−4 (−7, −1)	ND	0 (0)	2 (0.7)	−0.7 (−3, 0.7)	ND
Who discontinued due to serious AE	10 (4)	6 (2)	1 (−2, 5)	ND	0 (0)	1 (0.4)	−0.4 (−2, 1)	ND
Who discontinued due to serious drug-related AE	1 (0.4)	2 (0.7)	−0.4 (−2, 1)	ND	0 (0)	1 (0.4)	−0.4 (−2, 1)	ND
Who died[d]	4 (1)	1 (0.4)	1 (−1, 3)	.216	0 (0)	0 (0)	0 (−1.4, 1.4)	1.000

Data are no. (%) unless otherwise indicated. All treated patients were included in the safety analysis. All adverse events occurring during the study or within 14 days of study discontinuation through 13 July 2010 (the day when the last patient remaining in the study had their 156-week assessment) were counted. The frequencies of adverse events were not adjusted for the duration of follow-up.

Abbreviations: N = number of patients in each group; ND, not done (as the test was not prespecified in the data analysis plan).

[a] Difference (Δ) and 95% confidence interval (95% CI) was calculated as the response rate in the raltegravir group minus the response rate in the efavirenz group. The 95% CIs were calculated using the method of Miettinen and Nurminen (6).

[b] Tests of significance were performed on the percentage of patients with at least one adverse experience in a prespecified category per protocol. P values were generated using the Fisher's exact test.

[c] Determined by investigator to be possibly, probably, or definitely drug-related to any drug in the study regimen.

[d] None of the 5 deaths were judged to be drug-related.

[e] The discontinuations in the table refer to discontinuation of study medications (even if the patient remained in the study), whereas Figure 1 describes study discontinuations. The discordance between table and figure arises from patients who stopped study medication due to an adverse event but remained on study at the time of the week 96 analysis.

during the study occurred in raltegravir recipients. Compared to baseline, raltegravir was associated with smaller elevations of fasting lipid levels at week 144 than efavirenz. Measurement of body fat content by DEXA scanning showed proportionately more fat gain through 156 weeks in efavirenz than raltegravir recipients, but these numerical differences are hard to interpret because the subsets of patients entered in the DEXA substudy from each treatment arm were small, nonrandomized, and not strictly comparable in several relevant parameters at baseline.

Our results confirm that raltegravir combined with tenofovir/emtricitabine is a durably efficacious and generally well-tolerated combination for treatment-naive patients. However, because of the double-dummy design of STARTMRK, the regimens administered in the study were more complex than the corresponding regimens actually employed in clinical practice. In particular, this aspect of the rigorous blinded-study design would have negated any potential advantage of a 1-pill once-a-day regimen of efavirenz, tenofovir, and emtricitabine coformulated as Atripla in fostering strict compliance. Response rates with raltegravir were noninferior to efavirenz using the primary NC=F approach to missing data and superior to efavirenz when only treatment-related discontinuations were considered as failures. The overall adverse-event profile, including elevations in lipid parameters, was more favorable for patients receiving raltegravir than for patients receiving efavirenz through 3 years of treatment. No new safety signals or raltegravir-resistance mutations emerged during the extended follow-up through week 156. Along with efavirenz or boosted protease-inhibitor combinations, raltegravir given with tenofovir/emtricitabine can be considered among the preferred agents for long-term antiretroviral therapy of treatment-naive HIV-1–infected patients [8–10].

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Table 4. Cumulative Frequency of the Most Common[a] Specific Drug-Related[b] Clinical Adverse Events (CAE) of Moderate to Severe Intensity[c]

	Raltegravirgroup N = 281 n (%)	Efavirenzgroup N = 282 n (%)
Any moderate–severe CAE	59 (21)	98 (35)
Headache	11 (4)	14 (5)
Dizziness	4 (1)	18 (6)
Insomnia	10 (4)	11 (4)
Rash	0 (0)	21 (7)[d]
Nausea	8 (3)	10 (4)
Fatigue	5 (2)	8 (3)
Diarrhea	3 (1)	8 (3)

Data are no. of patients with the specified clinical adverse event (%).

Abbreviation: N = total no. of treated patients in each group; n (%) = number (percent) of patients in each category.

[a] MedDRA version 13.0 CAE terms present in ≥2% of either treatment group.

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

[c] All treated patients were included in the safety analysis. All adverse events occurring during the study or within 14 days of study discontinuation through 13 July 2010 (the day when the last patient remaining in the study completed their 156-week assessment) were counted. The frequencies of adverse events were not adjusted for the duration of follow-up.

[d] Includes ''Skin and Subcutaneous Tissue Disorders'' coded as unspecified ''rash'' (n = 8), ''generalized rash'' (n = 1), ''macular rash'' (n = 2), ''papular rash'' (n = 1), ''maculo-papular rash'' (n = 7), and ''drug eruption'' (n = 2).

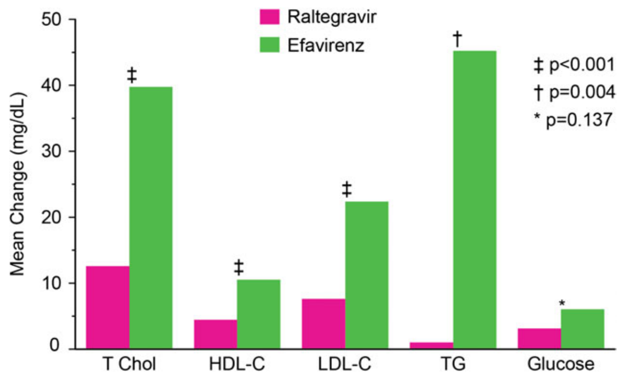

Figure 3. Mean changes in lipid and glucose concentrations at week 144 by treatment group. The graph shows the mean change from baseline to week 144 in total cholesterol (T CHOL), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), and triglycerides (TG) in mg/dL between the raltegravir group (left column) and the efavirenz group (right column). Each between-group comparison of lipid levels was significantly lower ($P < .005$) in raltegravir versus efavirenz recipients. The mean change in the total cholesterol:HDL-cholesterol ratio did not significantly differ between the raltegravir group (−0.20) and efavirenz group (0.04) ($P = .061$).

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The study was designed, managed, and analyzed by the sponsor in conjunction with external investigators. Authors had access to all study data upon request. This report was principally drafted by Drs Rockstroh, Wan, DiNubile, and Sklar. The presentation was critically reviewed multiple times and subsequently approved by each coauthor in its essentially final

Table 5. Frequency of Treatment-Emergent Grade 3/4 Laboratory Abnormalities

Prespecified laboratory tests	Toxicity criteria[a]	Raltegravir group N = 281 n/m (%)	Efavirenz group N = 282 n/m (%)
Absolute neutrophil count	<750 cells/μL	8/281 (2.8)	4/278 (1.4)
Hemoglobin	<7.5 gm/dL	3/281 (1.1)	2/278 (0.7)
Platelet count	<50,000/μL	0/276 (0.0)	1/276 (0.4)
Fasting total cholesterol	>300 mg/dL	0/276 (0.0)	14/267 (5.2)
Fasting LDL-cholesterol	≥190 mg/dL	5/271 (1.8)	23/262 (8.8)
Fasting triglycerides	>750 mg/dL	1/276 (0.4)	6/267 (2.2)
Fasting glucose	>250 mg/dL	4/274 (1.5)	2/266 (0.8)
Total bilirubin	>2.5 x ULN	3/281 (1.1)	0/279 (0.0)
Alkaline phosphatase	>5 x ULN	1/281 (0.4)	2/279 (0.8)
Aspartate aminotransferase	>5 x ULN	12/281 (4.3)	8/279 (2.9)
Alanine aminotransferase	>5 x ULN	6/281 (2.2)	7/279 (2.5)
Creatinine	≥1.9 x ULN	0/281 (0.0)	1/279 (0.4)

All treated patients with a laboratory abnormality exceeding the predefined limit of change through 13 July 2010 (the day when the last patient remaining in the study completed the week-156 visit) were included if the grade had worsened from baseline. Patients were classified by the highest grade abnormality.

Abbreviations: N, total no. of treated patients in each group; n, no. of patients with Grade 3 or 4 abnormalities of the prespecified laboratory test; M, no. of patients with results for the prespecified laboratory test; ULN, Upper Limit of Normal range.

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

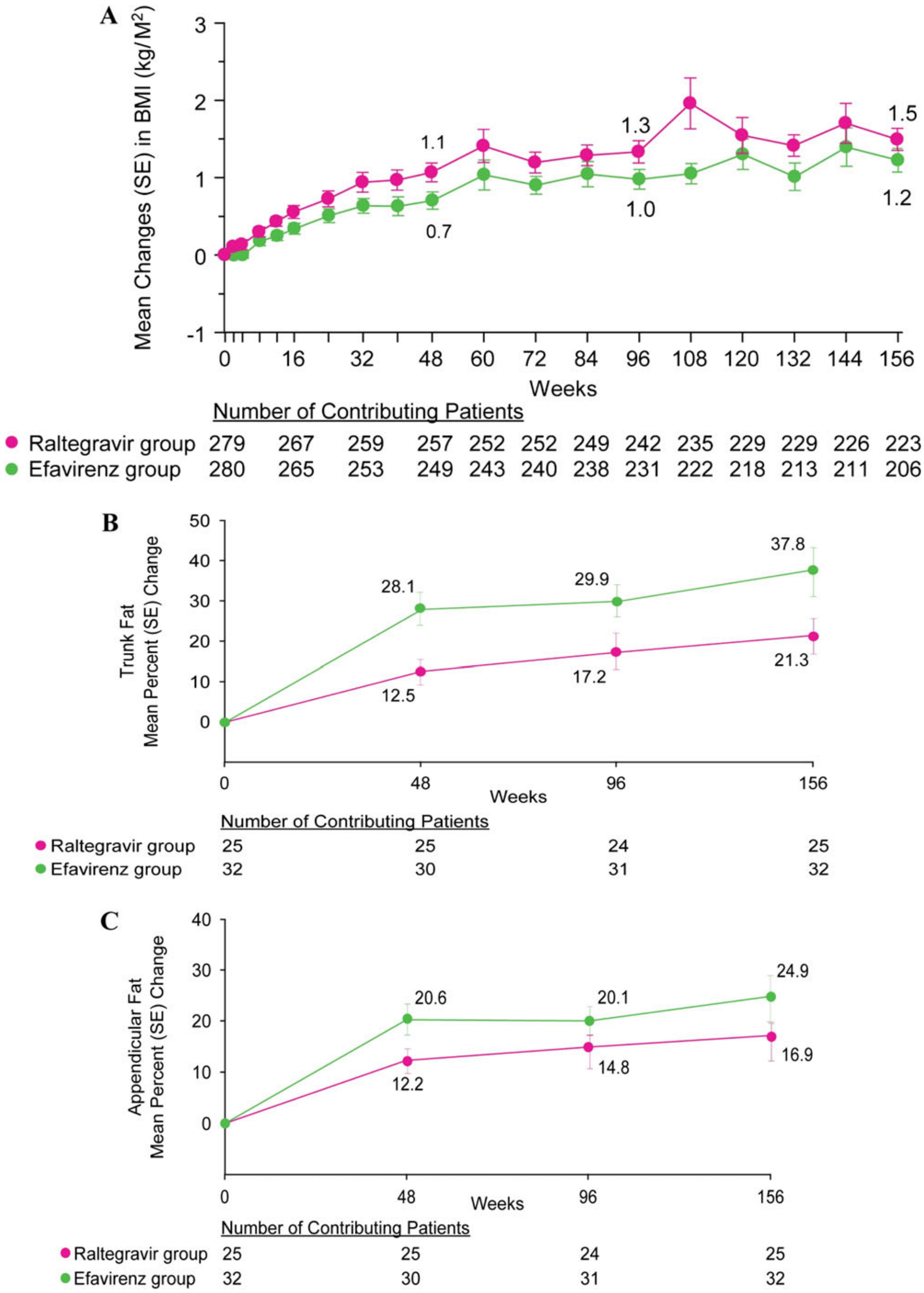

Figure 4. Mean changes in body mass index and fat composition over time by treatment group. The graphs display the mean change in kg/M^2 from baseline in BMI (*A*) and the mean percent change from baseline in trunk fat (*B*) and appendicular fat (*C*) over time. Measurements of body fat were made by Dual Energy X-ray Absorptiometry (DEXA) at weeks 48, 96, and 156. The mean percent change in fat content from baseline was calculated as the difference between the measurements at baseline and at the specified time point. The number of evaluable patients is shown for the treatment groups below each time point for the 57 patients in the DEXA substudy evaluable at week 156 (a more inclusive analysis is presented in Supplementary Figure S1; online only). Bars represent standard errors (SE). Repeat DEXA scans were used as the baseline measurement in 7 patients for whom the original baseline scans were not available. Baseline total fat content was 22.9 kg and 16.8 kg for the raltegravir and efavirenz participants, respectively ($\Delta = 6.1$ kg) with scans taken at week 156. The subsets of patients enrolled in the DEXA study from each treatment arm were small, nonrandomized, and not strictly comparable in several relevant parameters at baseline, confounding any between-treatment group comparisons.

form. The paper underwent formal review by the sponsor. The opinions expressed in the manuscript represent the collective views of the authors and do not necessarily reflect the official position of Merck.

Potential conflicts of interest. J. K. R. has been an investigator and a paid consultant for Merck, Gilead, Abbott, Bristol-Myers Squibb, Boehringer-Ingelheim, Bionor, Tibotec, GlaxoSmithKline, Pfizer, ViiV, Vertex, and

Roche. J. L. has been an investigator for Merck, Gilead, Pfizer, Schering, Tibotec, and Abbott, and has served as a paid consultant for Merck, Roche, and Abbott. E. D. has been an investigator for Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck, Roche Labs, Pfizer, Schering-Plough, Tibotec, and Vertex, and has served as a paid consultant for Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck, and Tibotec. M. S. S. has been an investigator for Merck, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Monogram, Pfizer, Tibotec, and ViiV, and has served as a paid consultant or speaker for Merck, Ardea, Avexa, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Pain Therapeutics, Pfizer, Tibotec, ViiV, and Vertex. A. L. has been an investigator, consultant or speaker for Merck, Bristol-Myers Squibb, Gilead, Pfizer, Tibotec, Roche, GlaxoSmithKline, Boehringer-Ingelheim, and Abbott. Coauthors who are employees of Merck (as indicated on the title page) may own stock and/or stock options in the company.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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