Durable Efficacy and Safety of Raltegravir Versus Efavirenz When Combined With Tenofovir/Emtricitabine in Treatment-Naive HIV-1–Infected Patients: Final 5-Year Results From STARTMRK

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Background: STARTMRK, a phase III noninferiority trial of raltegravir-based versus efavirenz-based therapy in treatment-naive patients, remained blinded until its conclusion at 5 years. We now report the final study results.

Methods: Previously untreated patients without baseline resistance to efavirenz, tenofovir, or emtricitabine were eligible for a randomized study of tenofovir/emtricitabine plus either raltegravir or efavirenz. Yearly analyses were planned, with primary and secondary end points stipulated at weeks 48 and 96, respectively. The primary efficacy outcome was the percentage of patients with viral RNA (vRNA) levels <50 copies per milliliter counting noncompleters as failures (NC=F). Changes from baseline CD4 count were computed using an observed-failure approach to missing data. No formal hypotheses were formulated for testing at week 240.

Results: Overall, 71 of 281 raltegravir recipients (25%) and 98 of 282 efavirenz recipients (35%) discontinued the study; discontinuations due to adverse events occurred in 14 (5%) and 28 (10%) patients in the respective groups. In the primary NC=F efficacy analysis at week 240, 198 of 279 (71.0%) raltegravir recipients and 171 of 279 (61.3%) efavirenz recipients had vRNA levels <50 copies per milliliter, yielding a treatment difference {Δ [95% confidence interval (CI)] = 9.5 (1.7 to 17.3)}. Generally comparable between-treatment differences were seen in both the protocol-stipulated sensitivity analyses and the prespecified subgroup analyses. The mean (95% CI) increments in baseline CD4 counts at week 240 were 374 and 312 cells per cubic millimeter in the raltegravir and efavirenz groups, respectively [Δ (95% CI) = 62 (22 to 102)]. Overall, significantly fewer raltegravir than efavirenz recipients experienced neuropsychiatric side effects (39.1% vs 64.2%, $P < 0.001$) or drug-related clinical adverse events (52.0% vs 80.1%, $P < 0.001$).

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Conclusions: In this exploratory analysis of combination therapy with tenofovir/emtricitabine in treatment-naive patients at week 240, vRNA suppression rates and increases in baseline CD4 counts were significantly higher in raltegravir than efavirenz recipients. Over the entire study, fewer patients experienced neuropsychiatric and drug-related adverse events in the raltegravir group than in the efavirenz group. Based on better virologic and immunologic outcomes after 240 weeks, raltegravir/tenofovir/emtricitabine seemed to have superior efficacy compared with efavirenz/tenofovir/emtricitabine.

Key Words: HIV, raltegravir, efavirenz, STARTMRK, treatment naive

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INTRODUCTION

Successful HIV treatment likely requires a lifelong commitment to medication.[1] Accordingly, long-term efficacy and safety data are essential to selecting therapy. Raltegravir-based regimens have been shown to be efficacious and generally well tolerated in treatment-naive and treatment-experienced patients with HIV infection.[2–8] STARTMRK was a randomized, blinded, double-dummy phase III trial of raltegravir with tenofovir/emtricitabine versus efavirenz with tenofovir/emtricitabine in treatment-naive HIV-infected adults.[2–5] Blinding was maintained for the entire 5-year duration of the study. The primary efficacy outcome was predefined as the percentage of patients in each treatment arm who achieved viral RNA (vRNA) levels <50 copies per milliliter. Yearly analyses were specified by protocol, with the primary analysis at week 48,[2] secondary analysis at week 96,[3] and exploratory analyses at weeks 156,[4] 192,[5] and 240.

At each interim time point studied during STARTMRK, raltegravir has proven noninferior to efavirenz using the primary noncompleter as failure (NC=F) approach to missing data specified by protocol.[2–5] After 192 weeks of combination therapy with tenofovir/emtricitabine, 76% and 67% of the respective raltegravir and efavirenz groups achieved vRNA levels <50 copies per milliliter, yielding a treatment difference [95% confidence interval (CI)] = 9 (2 to 16) consistent with the superiority of the raltegravir-based regimen over the efavirenz-based regimen.[5] Greater increments in CD4 cell counts from baseline to week 192 were observed with raltegravir than efavirenz [361 vs 301 cells/mm^3, Δ (95% CI) = 60 (24 to 95)]. Both regimens were reasonably well tolerated for the first 4 years of the study, with fewer drug-related adverse events reported in raltegravir than efavirenz recipients.[5]

In the current report, we present the final 5-year efficacy and safety results from the completed STARTMRK study, focusing on virologic and immunologic results (overall and in clinically relevant demographic and prognostic subgroups) and adverse event and discontinuation rates (including the frequency of neuropsychiatric side effects and changes in metabolic parameters).

METHODS

The STARTMRK trial (MK-0518 Protocol 021) was a blinded, double-dummy, randomized, active-control phase III clinical trial originally planned for 96 weeks but extended to 240 weeks.[2] Blinding was maintained for the entire duration of the study. The protocol was approved by the appropriate review committee at each site and executed in accordance with Good Clinical Practice guidelines.

Treatment-naive HIV-infected patients ≥ 18 years of age were eligible if their viral load was >5000 RNA copies per milliliter without genotypic resistance to tenofovir, emtricitabine, or efavirenz. Patients with stable chronic hepatitis could be enrolled if their serum aminotransferase levels were $\leq$5-fold the upper limit of the normal range, but patients with acute or decompensated chronic hepatitis were excluded. Patients were stratified by screening vRNA levels ($>50{,}000$ vs $\leq 50{,}000$ 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. After stratification, patients were randomly assigned in a 1:1 ratio to receive raltegravir or efavirenz, each given in combination with 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 bedtime. Patients were asked to complete diary cards for all study drugs, and the information on the diary cards was reviewed with the patient at each visit during the study. The site personnel also collected the used study drug bottles at each visit and counted the returned tablets to ensure information provided on the diary card was accurate. A patient was considered compliant on a given day if he/she took at least 1 tablet of study therapy on that day. To measure changes in body fat composition over time on study drugs, dual energy x-ray absorptiometry scans were performed on a subset of patients through week 156[4]; no further dual energy x-ray absorptiometry scanning was done after week 156.

Virologic response was defined as 2 consecutive vRNA levels <50 copies per milliliter measured at least 1 week apart. Virologic failure could represent either a nonresponse at week 24 (or premature discontinuation) or a confirmed rebound ≥ 50 vRNA copies per milliliter. Because of the nominal limit of the commercial resistance assays, genotyping was only planned to be performed on viral isolates from patients with vRNA levels >400 copies per milliliter at the time of failure.

Primary and secondary analyses were specified by protocol at weeks 48 and 96, respectively, with a -12% noninferiority margin. Standard outcomes were also to be analyzed in yearly exploratory analysis thereafter, including at the week 240 conclusion of the trial. For calculation of virologic response rates, the primary approach to handling missing data was to include all NC=F. An observed-failure (OF) approach, permitting assessment of efficacy without confounding by missing values resulting from discontinuations due to intolerability or nontreatment–related reasons, was used as a sensitivity analysis per protocol. The OF approach was also used for evaluating changes from baseline CD4 cell counts and for the subgroup analyses based on prespecified demographic and prognostic factors at baseline. With the OF approach, patients discontinued

for lack of efficacy were considered as failures thereafter. Likewise, if the most proximate vRNA level was ≥50 copies per milliliter prior to discontinuation for reasons unrelated to treatment, the patient was counted among the OFs even when the vRNA level was not confirmed (as required by the formal protocol definition of virologic failure). For the OF analysis of CD4 counts, baseline values were carried forward for patients who discontinued due to lack of efficacy, whereas patients who discontinued for other reasons were not included in the analyses thereafter. Another protocol-stipulated secondary analysis counted only the treatment-related discontinuations (but not discontinuations for other reasons) as failures (TRD=F). Snapshot analyses with windows of ±6 and ±12 weeks around the week 240 visit were also performed post hoc.

Although the protocol did not stipulate hypothesis testing at weeks 156, 192, or 240, an implicit fixed-sequence testing procedure was applied to control type I error given the multiplicity of time points for assessing noninferiority; if noninferiority was supported, a subsequent test for superiority was performed in a closed testing fashion.[9]

Safety data were collected for all randomized patients who were treated with ≥1 dose of any study drug from initiation of treatment until at least 14 days after permanent discontinuation of all study therapy. Investigators were asked to assess the potential relationship of each adverse event to the study regimen. For the purposes of this report, adverse experiences were classified as "drug related" if the investigator considered the adverse experience to be possibly, probably, or definitely related to any of the study medications alone or in combination. Investigators were also to grade the maximum intensity of individual adverse events as mild, moderate, or severe.

RESULTS

Patient Disposition

Baseline characteristics were similar for treated patients in both arms (see **Table S1**, **Supplemental Digital Content**, http://links.lww.com/QAI/A397). A total of 210 (74.5%) of the 281 patients treated with raltegravir and 184 (64.8%) of the 282 patients treated with efavirenz completed the entire 5-year study (Fig. 1A). Discontinuations due to adverse events occurred in 14 (5%) and 28 (10%) patients in the respective groups (see **Table S2**, **Supplemental Digital Content**, http://links.lww.com/QAI/A397). Time to discontinuation due to an adverse event was significantly shorter in the efavirenz than in the raltegravir group ($P = 0.023$) (Fig. 1B).

A total of 5 treated patients were excluded from the efficacy analyses at week 240. Two efavirenz recipients had missing data from week 240 visit but flanking vRNA measurements were <50 copies per milliliter. Two raltegravir recipients and 1 additional efavirenz recipient were off-treatment before week 240. The decision to exclude these 5 patients from the NC=F analysis was made before the clinical database was locked and unblinded. Among the 281 raltegravir recipients, 240 patients (85.4%) were considered 100% compliant with their regimen over the course of the study based on the protocol definition, whereas only 6 patients (2.1%) exhibited <90% adherence; among the 282 efavirenz recipients, 224 patients (79.4%) were considered 100% compliant through week 240, whereas 9 patients (3.2%) had <90% adherence.

Overall and Subgroup Efficacy

In the NC=F efficacy analysis at week 240, 198 of 279 raltegravir recipients (71.0%) and 171 of 279 efavirenz recipients (61.3%) had vRNA levels <50 copies per milliliter, yielding a treatment difference [Δ (95% CI) = 9.5 (1.7 to 17.3)] (Fig. 2A). Generally, comparable between-treatment differences were seen in the protocol-stipulated sensitivity analyses with both the OF and the treatment-related discontinuations as failures approaches to missing data (Table 1). Both prespecified sensitivity analyses at week 240 confirmed the noninferiority of raltegravir to efavirenz and were consistent with superiority of the raltegravir regimen over the efavirenz regimen demonstrated by the primary NC=F approach. Time to achieve virologic response was significantly shorter in the raltegravir group compared with the efavirenz group (log rank P value = 0.001). In patients experiencing virologic failure, comparable time to loss of virologic response was observed with each regimen. Mean (95% CI) changes from baseline CD4 counts at week 240 were 374 and 312 cells per cubic millimeter in the raltegravir and efavirenz groups, respectively [Δ (95% CI) = 62 (22 to 102)] (Fig. 2B).

Post hoc analyses of virologic suppression rates <50 RNA copies per milliliter likewise demonstrated noninferiority of raltegravir to efavirenz using either a 6-week or 12-week window around the scheduled week 240 visit. The snapshot analysis with a window of ±6 weeks did not demonstrate superiority because the result of the exclusion of 8 patients falling outside the window (6 came in too early and 2 came in too late) compared with the protocol-specified NC=F analysis that used the nominal visit data. By chance, all 8 excluded patients fell in the raltegravir group, with 7 having vRNA levels <50 copies per milliliter at their nominal week 240 visit. Because there were a greater number of patients with data available yet falling outside the 6-week window for the week 240 visit compared with prior time points, another snapshot analysis using a ±12 weeks window (extending the window to the preceding visit at week 228) was also performed at week 240; this analysis was consistent with both the noninferiority and the superiority of raltegravir compared with efavirenz.

Subgroup analyses at week 240 using an OF approach for missing data demonstrated consistent virologic and immunologic treatment effects between groups across key prespecified demographic and baseline prognostic factors, including gender, age, race, vRNA level (≤100,000 vs >100,000 copies/mL), CD4 count (≤200 vs >200 cells/mm^3), HIV-1 subtype (B vs non-B clades), and hepatitis B and/or C coinfection (Fig. 3). A subsequent post hoc analysis of virologic response rates broken down by baseline vRNA levels ≤250,000 and >250,000 copies per milliliter for each treatment group is presented in **Table S3** (see **Supplemental Digital Content**, http://links.lww.com/QAI/A397).

Emergent Resistance

Cumulatively through week 240, 114 patients experienced virologic failure, including 23 of 55 raltegravir

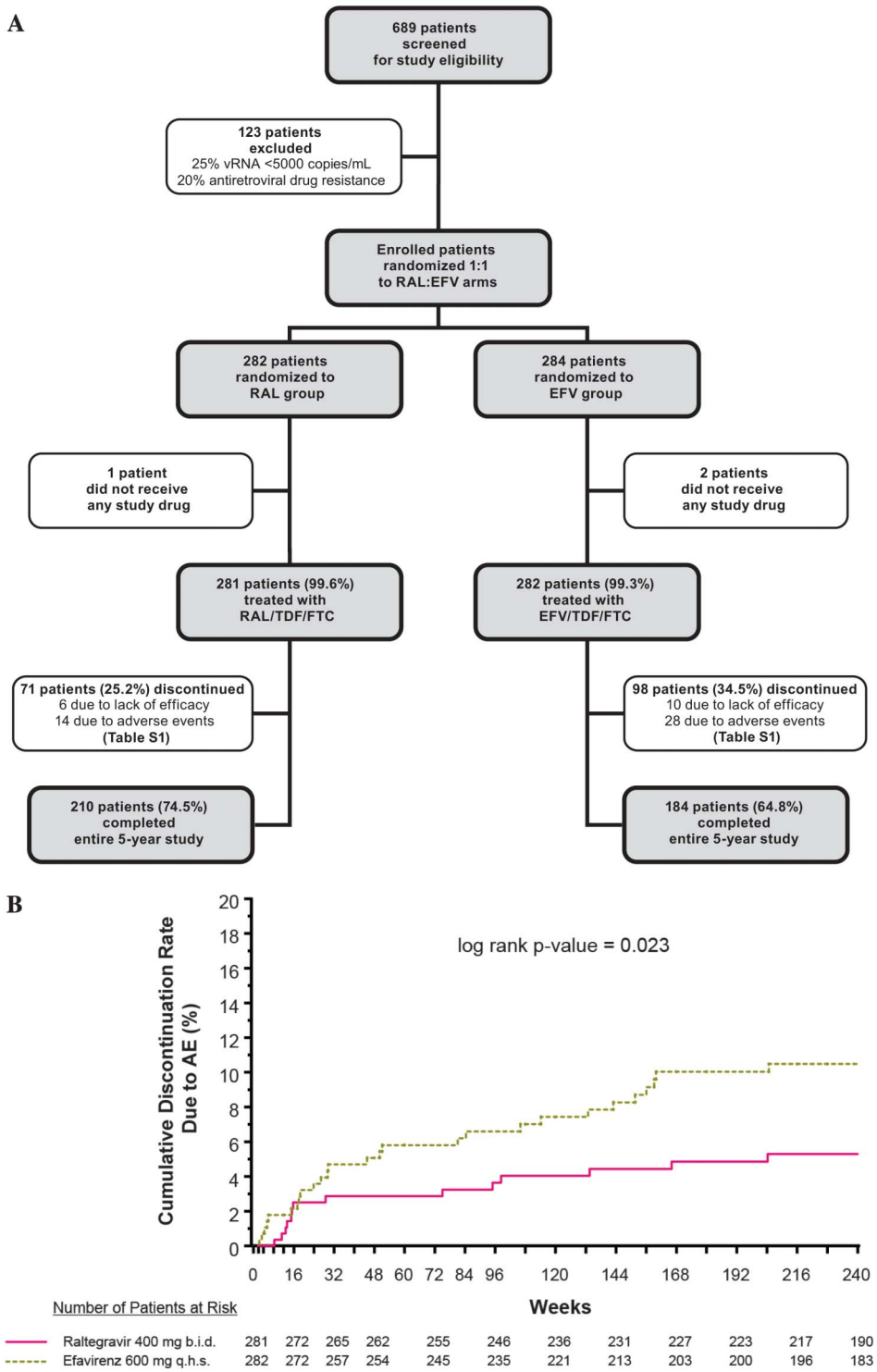

FIGURE 1. Patient disposition. A, CONSORT diagram. **Supplemental Digital Content 1** (see **Table S1**, http://links.lww.com/QAI/A397) presents a comprehensive list of the reasons for discontinuation from the study). B, Time to discontinuation due to an adverse event (AE).

recipients and 20 of 59 efavirenz recipients with vRNA levels >400 copies per milliliter, allowing virus amplification for resistance testing (see **Table S4**, **Supplemental Digital Content**, http://links.lww.com/QAI/A397). Raltegravir-resistant virus was demonstrated in 4 of the 23 patients in the raltegravir group with sequencing data (1 case each showing Q148H + G140S, Q148R + G140S, Y143Y/H + L74L/M + E92Q +T97A, and Y143R); in 3 of these 4 cases, the viruses had dual raltegravir- and emtricitabine-resistance but remained sensitive to tenofovir. Emtricitabine resistance was detected in 3 additional cases (including in 1 patient with raltegravir susceptible virus and in 2 other patients where the integrase gene was not amplified). Efavirenz-resistant virus was demonstrated in 10 of the 17 patients in the efavirenz group with sequencing data (all

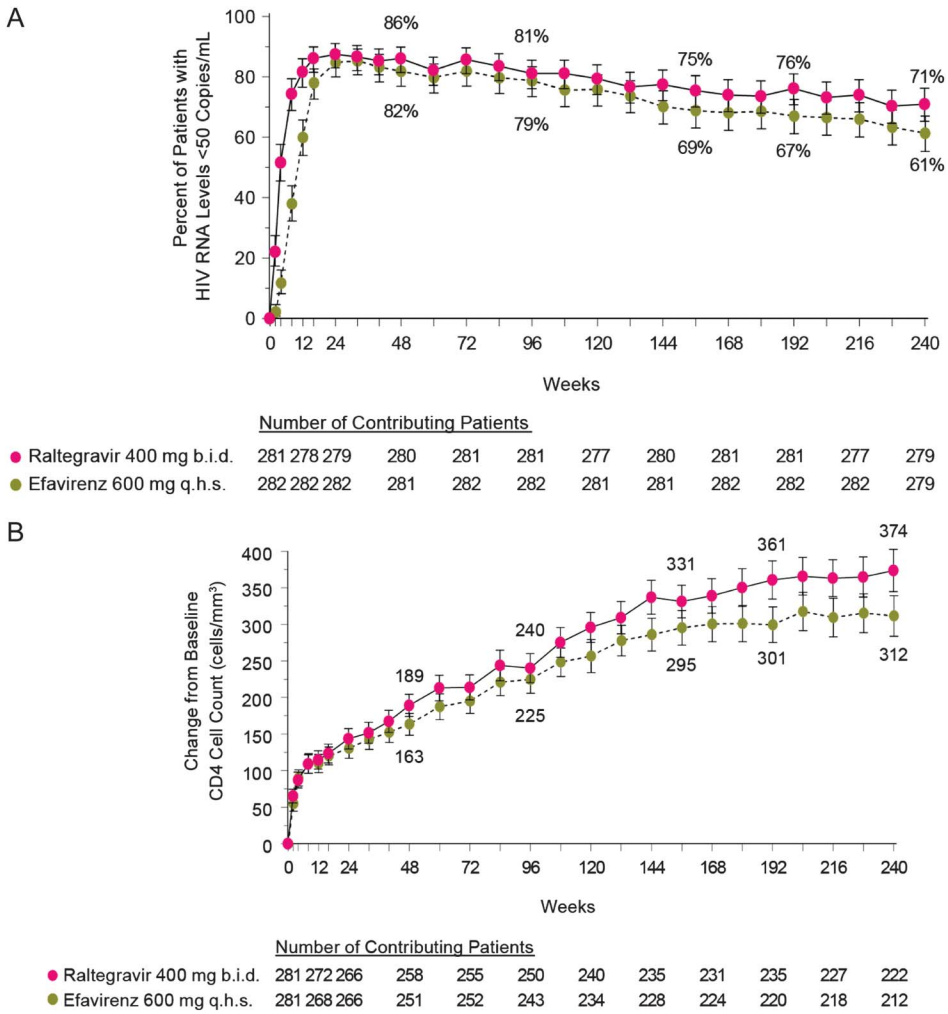

FIGURE 2. A, Time course of virologic response rates (measured from randomization to the first of 2 vRNA levels <50 copies/mL sampled at least a week apart). B, CD4 cell count increments by treatment group. Missing data were handled by NC=F approach for virologic response rates and by an OF approach for CD4 count increments.

had the K103N substitution, with K103N as the sole mutation in 3 instances); the viruses were also emtricitabine resistant but susceptible to tenofovir in 3 of these 10 cases and resistant to both emtricitabine and tenofovir in 1 case. In 2 additional efavirenz recipients, only emtricitabine resistance was detected.

During the most recently analyzed interval from week 192 to week 240, 7 additional patients (3 raltegravir recipients and 4 efavirenz recipients) met the protocol definition of virologic failure. Resistance was not detected to any drugs in the regimen in any of the 3 raltegravir failures, whereas isolated efavirenz resistance was detected in the 3 evaluable efavirenz failures.

Adverse Events

There were no significant differences in overall adverse events between the 2 groups (Table 2). However, drug-related clinical adverse events were reported in 146 raltegravir recipients (52.0%) versus 226 efavirenz recipients (80.1%) ($P < 0.001$). The most common drug-related adverse events were gastrointestinal and neuropsychiatric disorders (Table 3). The raltegravir group had significantly fewer patients with reported nervous system adverse experiences (39.1%) compared with the efavirenz group (64.2%) as measured by the cumulative proportion of patients with 1 or more neuropsychiatric adverse experiences by week 240 ($P < 0.001$). Neuropsychiatric symptoms first seemed early in the course of treatment (see **Figure S1**, **Supplemental Digital Content**, http://links.lww.com/QAI/A397). Overall, new or recurrent malignancies were diagnosed in 5 (1.8%) raltegravir recipients and 2 (0.7%) efavirenz recipients.

Laboratory adverse events were reported in 56 patients (19.9%) who received raltegravir and 77 patients (27.3%) who received efavirenz. Two patients (both efavirenz recipients) had serious laboratory adverse experiences. Two patients (both efavirenz recipients) discontinued the study because of drug-related laboratory adverse experiences.

Five patients in each treatment group died during the study. None of the deaths were considered drug related. Causes of death in raltegravir recipients were: Kaposi sarcoma, metastatic lung cancer, malignant lung neoplasm, cerebral hemorrhage, and alcohol poisoning with multidrug toxicity. Causes of death in efavirenz recipients were plasmablastic lymphoma, hemoptysis, sepsis, pneumonia

TABLE 1. Sensitivity Analyses of Virologic Efficacy (vRNA Level <50 copies/mL) at Week 240*

Different Approaches to Handling Missing Data	Response by Treatment Group: Responders/Evaluable Patients†		Treatment Effect: Difference Estimates‡			
	Raltegravir Group	Efavirenz Group	Between-Group Difference	95% CI	*P* Value for Noninferiority§	Superiority Concluded§
Protocol-specified primary analysis						
Noncompletor=failure	198/279 (71.0)	171/279 (61.3)	9.5	1.7–17.3	<0.001	Yes
Protocol-specified secondary analyses						
Treatment-related discontinuation=failure	198/236 (83.9)	171/239 (71.5)	12.4	4.9–19.8	<0.001	Yes
Observed failure	198/222 (89.2)	171/212 (80.7)	8.6	1.9–15.5	<0.001	Yes
Post hoc exploratory analyses						
Snapshot with window of ±6 weeks‖	186/281 (66.2)	168/282 (59.6)	6.6	−1.4 to 14.5	<0.001	No
Snapshot with window of ±12 weeks¶	199/281 (70.8)	177/282 (62.8)	8.1	0.3–15.8	<0.001	Yes

*Formal hypothesis testing was not specified at week 240 by the protocol.

†Number of evaluable patients in each treatment group according to the specified approach to handling missing data.

‡The 95% CIs and *P* values for treatment differences were calculated using weights proportional to the size of each stratum (screening vRNA level >50,000 or ≤50,000 copies/mL).

§Raltegravir would be considered noninferior to efavirenz if the lower bound of the 95% CI for the difference in response rates was above −12% and superior to efavirenz if the entire 95% CI was >0.

‖The snapshot analysis with a window of ±6 weeks around the week 240 visit (as requested at earlier time points by the Food and Drug Administration) resulted in the exclusion of 8 patients falling outside of window (6 came in too early and 2 came in too late) compared with the protocol-specified NC=F analysis that used the nominal visit data. All 8 excluded patients were in the raltegravir group, with 7 having vRNA levels <50 copies per milliliter at their nominal week 240 visit.

¶For a long-term time point, the chance of falling outside a given window increases relative to earlier time points. Therefore, as there were a greater number of patients falling outside the 6-week window for the week 240 visit compared with previous time points, an analysis using a ±12 weeks window (extending the window to the prior visit at week 228) was also performed at week 240 after the data were unblinded to further assess the robustness of the findings.

and septic shock complicating leukemia, and an unknown cause. All adverse events of moderate or severe intensity irrespective of causality are listed in **Table S5** (see **Supplemental Digital Content**, http://links.lww.com/QAI/A397).

The safety profile in the 18 raltegravir and 16 efavirenz patients with hepatitis B and/or hepatitis C coinfection at baseline was comparable with patients without baseline hepatitis infection. In both treatment groups, transaminase

TABLE 2. Summary of Adverse Events During and for 14 Days After Study Treatment

	Raltegravir Group (N = 281) n (%)	Efavirenz Group (N = 282) n (%)	Difference* (Raltegravir − Efavirenz) % (95% CI)	*P*
No. patients				
With 1 or more adverse experiences	271 (96.4)	276 (97.9)	−1.4 (−4.6 to 1.5)	0.325
With no adverse experience	10 (3.6)	6 (2.1)	1.4 (−1.5 to 4.6)	0.325
With drug-related† adverse experiences	146 (52.0)	226 (80.1)	−28.2 (−35.5 to −20.6)	<0.001
With serious adverse experiences‡	57 (20.3)	57 (20.2)	0.1 (−6.6 to 6.7)	1.000
With serious drug-related‡ adverse experiences	8 (2.8)	7 (2.5)	0.4 (−2.6 to 3.3)	0.801
Who died§	5 (1.8)	5 (1.8)	0.0 (−2.5 to 2.6)	1.000
Discontinued due to adverse experiences	14 (5.0)	25 (8.9)	−3.9 (−8.3 to 0.3)	0.096
Discontinued due to drug-related† adverse experiences	3 (1.1)	14 (5.0)	−3.9 (−7.2 to −1.2)	‖
Discontinued due to serious adverse experiences	11 (3.9)	10 (3.5)	0.4 (−3.0 to 3.8)	‖
Discontinued due to serious drug-related† adverse experiences	1 (0.4)	2 (0.7)	−0.4 (−2.2 to 1.3)	‖

*Tests of significance were performed on the percentage of patients with at least 1 adverse experience in the category. No adjustments for multiplicity were made for the evaluation of safety.

†Determined by the investigator to be possibly, probably, or definitely drug related.

‡Among the 114 patients experiencing serious adverse events, a total of 191 postrandomization serious clinical adverse experiences were reported. In addition, 1 serious drug-related adverse event of B-cell lymphoma was reported in the efavirenz group but does not seem in the table because it occurred >14 days after study drug discontinuation. Three serious nondrug–related adverse events in 2 patients were also not included in the table because they occurred >14 days after study drug discontinuation: bradycardia in an efavirenz and intervertebral disc protrusion and cervical myelopathy in a raltegravir recipient.

§None of the adverse experiences resulting in death were determined by the investigators to be drug related.

‖Not prespecified for statistical analysis.

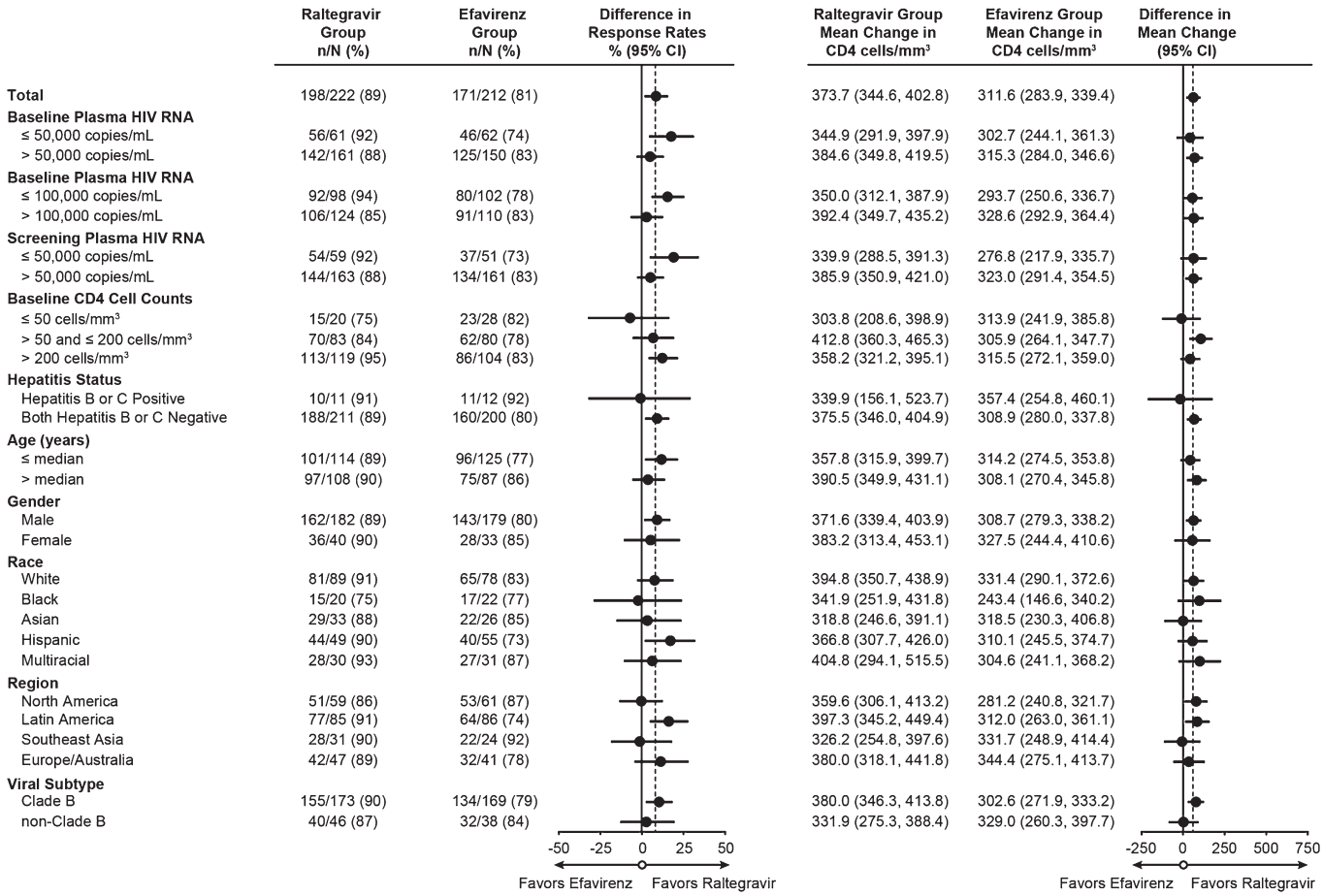

FIGURE 3. Forest plots of week 240 virologic response rates (percent of patients with confirmed vRNA level <50 copies/mL) and CD4 count increments from baseline (cells/mm^3) by treatment group. Subgroup efficacy analyses based on demographic subpopulations and prognostic factors at baseline are shown. The left side of the figure gives the proportion of patients with vRNA levels <50 copies per milliliter; the right side gives the increase in CD4 cells per cubic millimeter from baseline. Missing data were handled by the OF approach. The overall results are presented at the top of the plots and represented by a vertical dotted line for convenient reference. The solid line indicates no difference between the treatment arms. The subgroups for analysis were prespecified by protocol. The median age at entry was 36 years for the raltegravir group and 37 years for the efavirenz group. The data analysis plan did not include formal hypothesis testing by subgroup. N, number of evaluable patients in the OF population at week 240; n, number of patients with vRNA level <50 copies per milliliter at week 240.

elevations developed more commonly among coinfected than HIV-monoinfected patients but were mostly low grade and without apparent clinical significance.

Metabolic Parameters

At baseline, 5% of patients in the raltegravir group and 3% of patients in the efavirenz group were being treated with lipid-lowering medications. Among patients not on lipid-lowering therapy at baseline, treatment for this purpose was initiated in 13 raltegravir recipients and 34 efavirenz recipients. Through week 240, serum lipid-reducing agents were used in 9% of patients on raltegravir and 15% on efavirenz.

Increases in fasting lipid levels from baseline were significantly lower at week 240 ($P < 0.005$) in raltegravir than efavirenz recipients for serum triglycerides, total cholesterol, HDL cholesterol, and LDL cholesterol (see **Table S6**, **Supplemental Digital Content**, http://links.lww.com/QAI/A397). The mean change in the total cholesterol:HDL cholesterol ratio did not significantly differ between the raltegravir group (−0.22) and efavirenz group (−0.08) at week 240 ($P = 0.375$). No significant change in fasting glucose levels from baseline was observed between the treatment groups at week 240. Baseline and end-of-treatment levels are displayed in the context of recommended treatment targets in **Figure S2**, (see **Supplemental Digital Content**, http://links.lww.com/QAI/A397).

DISCUSSION

STARTMRK represents the longest duration of double-blind follow-up of any study of an integrase inhibitor. Overall virologic response rates and mean increments in baseline CD4 cell counts were higher with the raltegravir-based regimen compared with the control efavirenz-based regimen at the 5-year conclusion of the STARTMRK trial of combination antiretroviral therapy for treatment-naive patients. Because the

TABLE 3. Number (%) of Patients With Specific Drug-Related Clinical Adverse Experiences Reported in ≥5% of Either Treatment Group

	Raltegravir Group (N = 281) n (%)	Efavirenz Group (N = 282) n (%)
Gastrointestinal disorders	61 (21.7)	83 (29.4)
Diarrhea	15 (5.3)	28 (9.9)
Flatulence	10 (3.6)	14 (5.0)
Nausea	25 (8.9)	31 (11.0)
General disorders	28 (10.0)	47 (16.7)
Fatigue	12 (4.3)	25 (8.9)
Nervous system disorders	52 (18.5)	140 (49.6)
Dizziness	22 (7.8)	99 (35.1)
Headache	26 (9.3)	40 (14.2)
Somnolence	3 (1.1)	21 (7.4)
Psychiatric disorders	52 (18.5)	87 (30.9)
Abnormal dreams	19 (6.8)	37 (13.1)
Insomnia	21 (7.5)	23 (8.2)
Nightmare	8 (2.8)	15 (5.3)
Skin and subcutaneous tissue disorders	17 (6.0)	63 (22.3)
Rash	3 (1.1)	23 (8.2)

Adverse event terms are taken verbatim from MedDRA, version 14.1. Patients experiencing adverse events reported by the site investigators as possibly, probably, or definitely related to any drug in the study regimen are tabulated if reported in ≥5% of either treatment group. Although a patient may have had ≥1 clinical adverse experience, the patient is counted only once within an organ system category. The same patient may be tabulated in multiple different categories.

95% CI around the difference in the point estimates of suppression rates <50 vRNA copies per milliliter for raltegravir minus efavirenz fell entirely above 0 at week 240, the results from these exploratory analyses are consistent with statistically superior long-term efficacy of raltegravir with tenofovir/emtricitabine over the comparator efavirenz-based regimen. These findings were confirmed by both protocol-stipulated sensitivity analyses at week 240. Subsequent to week 96, no further raltegravir recipients developed virologic failure associated with detectable viral integrase mutations; in contrast, 5 additional efavirenz recipients experienced virologic failure with detectable resistance to efavirenz.[4,5]

Both antiretroviral regimens were generally well tolerated,[8] but study discontinuations precipitated by adverse experiences occurred less frequently in the raltegravir group than in the efavirenz group. Overall, drug-related clinical adverse events were reported less often with the raltegravir-based than the efavirenz-based study regimen. Especially early in the study, fewer raltegravir than efavirenz recipients developed neuropsychiatric symptoms.[8,10]

The efficacy advantage of raltegravir over efavirenz was maintained in the OF analysis, implying that the observed treatment differences were potentially in part due to virologic effects and not simply to differential tolerability. For the most part, consistent virologic and immunologic effects between treatment groups persisted at week 240 across the examined demographic characteristics and prognostic factors at baseline prespecified per protocol.[5,11,12] Greater CD4 cell increases were observed with raltegravir than efavirenz overall and in most subgroups. Although the small sample sizes in the subgroup analyses are associated with less precise efficacy estimates, raltegravir with tenofovir/emtricitabine provided higher response rates than the efavirenz combination across nearly all clinically relevant baseline subgroups within this treatment-naive population.

A drawback of rigorously controlled clinical trials is that they often must of necessity diverge to some degree from real-world practice. In STARTMRK, the comparator efavirenz/tenofovir/emtricitabine regimen was not administered as the coformulated Atripla because of the blinded double-dummy study design, thus negating any potential advantage of this simple and convenient 1-pill once-daily regimen commonly used in routine clinical practice.

Raltegravir combined with tenofovir/emtricitabine in treatment-naive patients produced durable viral suppression and immune restoration through 5 years of therapy. In this exploratory analysis of combination therapy with tenofovir/emtricitabine in treatment-naive patients at week 240, HIV suppression rates <50 vRNA copies per milliliter and CD4 cell increments were significantly higher in the raltegravir than in the efavirenz group. Generally consistent virologic and immunologic effects between treatment groups were maintained within the examined baseline demographic subpopulations and prognostic subgroups. At both 4 and 5 years, the raltegravir regimen exhibited persistently superior virologic and immunologic efficacy compared with the efavirenz regimen used in STARTMRK.[5] Over the course of the entire 5-year study, raltegravir-based therapy maintained a favorable safety profile relative to efavirenz-based therapy, with fewer reported patients with neuropsychiatric side effects and drug-related adverse events.[2–5,8] Raltegravir in combination with tenofovir/emtricitabine offers an efficacious and well-tolerated option for the initial therapy of treatment-naive HIV-infected patients irrespective of baseline viral load.[1]

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