MAJOR ARTICLE

Maraviroc versus Efavirenz, Both in Combination with Zidovudine-Lamivudine, for the Treatment of Antiretroviral-Naive Subjects with CCR5-Tropic HIV-1 Infection

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(See the editorial commentary by Sax, on pages 797–799.)

Background. The MERIT (Maraviroc versus Efavirenz in Treatment-Naive Patients) study compared maraviroc and efavirenz, both with zidovudine-lamivudine, in antiretroviral-naive patients with R5 human immunodeficiency virus type 1 (HIV-1) infection.

Methods. Patients screened for R5 HIV-1 were randomized to receive efavirenz (600 mg once daily) or maraviroc (300 mg once or twice daily) with zidovudine-lamivudine. Coprimary end points were proportions of patients with a viral load <400 and <50 copies/mL at week 48; the noninferiority of maraviroc was assessed.

Results. The once-daily maraviroc arm was discontinued for not meeting prespecified noninferiority criteria. In the primary 48-week analysis ($n = 721$), maraviroc was noninferior for <400 copies/mL (70.6% for maraviroc vs 73.1% for efavirenz) but not for <50 copies/mL (65.3% vs 69.3%) at a threshold of −10%. More maraviroc patients discontinued for lack of efficacy (11.9% vs 4.2%), but fewer discontinued for adverse events (4.2% vs 13.6%). In a post hoc reanalysis excluding 107 patients (15%) with non-R5 screening virus by the current, more sensitive tropism assay, the lower bound of the 1-sided 97.5% confidence interval for the difference between treatment groups was above –10% for each end point.

Conclusions. Twice-daily maraviroc was not noninferior to efavirenz at <50 copies/mL in the primary analysis. However, 15% of patients would have been ineligible for inclusion by a more sensitive screening assay. Their retrospective exclusion resulted in similar response rates in both arms

Trial registration. ClinicalTrials.gov identifier: (NCT00098293).

Although the prognosis for patients with human immunodeficiency virus type 1 (HIV-1) infection has improved dramatically over the past decade, challenges remain. Current antiretroviral agents have problems of low genetic barriers to resistance, cross-class resistance, or toxicity. Furthermore, the prevalence of transmitted HIV resistant to established agents is significant, with up to 14% of recently infected treatment-naive patients harboring drug-resistant HIV-1 [1]. Thus, there is a need for additional therapeutic options with novel mechanisms of action and acceptable tolerability profiles.

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Initial approval of the CCR5 antagonist maraviroc [2] was for treatment-experienced adults with R5 HIV-1 infection and was based on the results of the MOTIVATE (Maraviroc versus Efavirenz in Treatment-Naive Patients) studies [3, 4]. However, the prevalence of R5 virus is highest in treatment-naive individuals, with 81%–88% harboring R5 HIV-1 [5–8]. Thus, a CCR5 antagonist as a component of initial highly active antiretroviral therapy (HAART) has the potential to provide benefit to a large proportion of the treatment-naive population.

The phase 2b/3 MERIT (Maraviroc versus Efavirenz in Treatment-Naive Patients) study evaluated the efficacy and safety of maraviroc versus efavirenz as components of HAART in treatment-naive patients. Because maraviroc appears to have significant virologic activity against R5 HIV-1 only [9], its use requires screening to confirm infection with R5 virus. The original Trofile assay (Monogram Biosciences) [10], which is no longer available, was used to determine HIV-1 tropism in patients screened for phase 2 and 3 studies of maraviroc. After an enhanced version of this assay with greater sensitivity for detecting minority CXCR4-using strains (ie, either dual or mixed tropic [D/M] strains or CXCR4-tropic strains) became available [11, 12], screening samples from MERIT were retested, and a descriptive post hoc reanalysis of the major end points was performed. Both the primary 48-week analyses and the post hoc reanalysis of the MERIT study are presented here.

METHODS

Study subjects. The study enrolled treatment-naive patients ⩾16 years of age who were infected with R5 HIV-1, had a plasma viral load of ⩾2000 RNA copies/mL, and showed no evidence of viral resistance to zidovudine, lamivudine, or efavirenz.

Study design. MERIT is an ongoing double-blind, double-dummy study that is being conducted in North and South America, Europe, South Africa, and Australia. Informed consent was obtained and eligibility assessed at the screening visit. Screening evaluations included HIV-1 tropism testing (original Trofile assay) and HIV-1 resistance testing (PhenoSense GT; Monogram Biosciences). Eligible patients were randomized to receive coformulated zidovudine-lamivudine twice daily with either 300 mg of maraviroc once daily, 300 mg of maraviroc twice daily, or 600 mg of efavirenz once daily and were stratified by geographic location (Northern or Southern Hemisphere) and screening viral load ($<1 \times 10^5$ or $\geqslant 1 \times 10^5$ HIV-1 RNA copies/mL).

Protocol-defined treatment failure consisted of failure to reach an HIV-1 RNA level of <400 copies/mL at week 24 or as any of the following (confirmed by a second consecutive measurement): an increase in HIV-1 RNA level to ⩾3 times baseline at week 2 or thereafter; an HIV-1 RNA level of ⩾1000 copies/mL after 2 consecutive visits with a level of <400 copies/mL; or a <1 $\log_{10}$ decrease from baseline in HIV-1 RNA level at week 4 or thereafter. HIV-1 tropism and resistance testing was performed in patients who met the failure criteria. An analysis of resistance at treatment failure is presented for a subset of patients with virologic failure by the time to loss of virologic response (TLOVR) algorithm (<50 copies/mL threshold) who had a plasma viral load of >500 copies/mL and virus at failure that gave an R5 tropism result by the enhanced Trofile assay. For zidovudine, lamivudine, and efavirenz, genotypic resistance analyses were based on mutations defined by the International AIDS Society–USA [13]. Maraviroc resistance was evaluated using the PhenoSense Entry assay (Monogram Biosciences), with plateaus in maximum percentage inhibition of <95% defining reduced maraviroc susceptibility [14].

Periodic data and safety monitoring board assessments were made using partially blinded data tables provided by an independent statistical data analysis center (Covance CAPS, Maidenhead, United Kingdom). A formal interim analysis was undertaken at week 16 to evaluate the maraviroc arms for noninferiority to efavirenz. Investigators and patients remained blinded until the last patient completed week 96.

The study was approved by the institutional review boards or independent ethics committees of each participating center and was conducted in compliance with the principles originating or derived from the Declaration of Helsinki and with all International Conference on Harmonization Good Clinical Practice guidelines and local regulatory requirements.

Statistical analysis. Efficacy data were analyzed for all patients who received at least 1 dose of study medication. For the interim analysis, noninferiority of either maraviroc dose versus efavirenz depended on (1) the upper bound of the 1-sided 97.5% confidence interval (CI) of the time-averaged difference in HIV-1 RNA level through week 16 being <0.5 $\log_{10}$ copies/mL and (2) the lower bound of the 97.5% CI for the stratification-adjusted difference in proportions <400 copies/mL at week 16 being above −20%.

The principal study objective was to assess whether the antiviral activity of 300 mg of maraviroc twice daily or once daily was noninferior to 600 mg of efavirenz once daily when given with zidovudine-lamivudine. Coprimary end points were the proportion of patients in each arm with <400 HIV-1 RNA copies/mL and <50 copies/mL at week 48. Missing values were classified as nonresponses.

The total sample size of 1071 patients (three arms randomized 1:1:1) was calculated to provide 80% power to demonstrate noninferiority between each maraviroc arm and efavirenz at <50 copies/mL and 86% power at <400 copies/mL. These calculations were based on assumptions that 75% of patients in each arm would achieve <50 copies/mL at week 48, a 1-sided significance level of .0125 based on a Bonferroni correction for the 2 planned comparisons (once-daily maraviroc vs

efavirenz and twice-daily maraviroc vs efavirenz), and a noninferiority margin of −10%. Following the outcome of the interim analysis, a prespecified 1-sided 97.5% CI was applied to the stratification-adjusted difference in proportions meeting the week 48 end points between the twice-daily maraviroc arm and the efavirenz arm. Noninferiority was defined as the lower bound of this 97.5% CI being above −10%. A step-down procedure was applied, with proportions of patients with <50 copies/mL evaluated only if noninferiority was demonstrated for <400 copies/mL.

Secondary objectives included comparing the treatment regimens for safety and tolerability, reductions from baseline in HIV-1 RNA level, $CD4^+$ cell count changes from baseline (using last-observation-carried-forward imputation), and HIV-1 genotype, phenotype, and tropism at treatment failure.

Post hoc reanalysis. A descriptive post hoc reanalysis repeated these analyses for only those patients whose screening samples retrospectively retested as R5 by the current Trofile assay, which has been enhanced to increase detection of minor CXCR4-using variants (100% detection when they comprise 0.3% of the viral population, as opposed to 10% for the original Trofile assay) [11, 12]. Rescreening was performed by Monogram Biosciences, using stored samples generated from the original screening amplifications. No study outcome data or treatment assignments were available to Monogram Biosciences. Patients whose samples retested as non-R5 were excluded from the reanalysis.

RESULTS

Patient characteristics and disposition. Of 1730 patients screened, 453 (26%) did not have an evaluable tropism result (original Trofile assay). Of the remaining 1277, 217 (17%) were excluded for a result indicating a CXCR4-using virus. Other reasons for screening failure included an HIV-1 RNA level of <2000 copies/mL and resistance to zidovudine, lamivudine, or efavirenz. The remaining 917 were randomized, and 895 received at least 1 dose of study medication (Figure 1).

At the interim analysis, 205 patients had been receiving study medication for ⩾16 weeks. The stratification-adjusted mean time-averaged difference for once-daily maraviroc ($n = 68$) versus efavirenz ($n = 69$) was −2.21 versus −2.45 $\log_{10}$ copies/mL (difference, 0.24 $\log_{10}$ copies/mL [97.5% CI upper bound, 0.51 $\log_{10}$ copies/mL]), and the proportions of patients with <400 RNA copies/mL were 77.9% versus 88.4% (adjusted difference, −10.5% [97.5% CI lower bound, −25.9%]). Because these bounds fell outside the prespecified thresholds for noninferiority to efavirenz, the data and safety monitoring board recommended discontinuation of the once-daily maraviroc arm. Enrollment to the 2 remaining arms continued.

Of 740 patients randomized, 721 (twice-daily maraviroc, 360; once-daily efavirenz, 361) were included in the 48-week analysis, including 1 patient with a D/M screening result randomized (to maraviroc) in error. Baseline characteristics were balanced between arms (Table 1). The majority of black (181/232 [78%]) and female (130/181 [72%]) patients were located in the Southern Hemisphere, and 45% of the patients in this geographic stratum (versus 38% in the Northern Hemisphere) had a screening viral load of $>1 \times 10^5$ copies/mL.

The overall number of discontinuations was similar between arms (maraviroc, 97; efavirenz, 91) (Figure 1). However, discontinuations for adverse events were more than 3-fold higher during efavirenz therapy (13.6% vs 4.2%), whereas there were more discontinuations for lack of efficacy during maraviroc therapy (11.9% vs 4.2%).

Virologic and immunologic outcomes. The proportions of patients with an HIV-1 RNA level of <50 copies/mL by study visit and week 48 treatment differences for the coprimary end points are shown in Figure 2*A*. Maraviroc noninferiority to efavirenz was established for the <400 copies/mL end point: 70.6% of patients receiving maraviroc versus 73.1% of patients receiving efavirenz responded, and the lower bound of the adjusted 1-sided 97.5% CI was above −10%. For the <50 copies/mL end point, the proportions responding were 65.3% versus 69.3%, respectively, and the noninferiority criterion was not met.

Although a similar proportion of patients in both arms responded in the Northern Hemisphere, a lower proportion of patients responded to maraviroc in the Southern Hemisphere (Figure 2*D*). Corresponding differences were also observed according to race and clade, with lower response rates for maraviroc therapy among black patients and those with non–subtype B infections (Figure 2*E*).

Patients receiving maraviroc demonstrated greater increases in $CD4^+$ cell count than did those receiving efavirenz, with mean changes in $CD4^+$ count from baseline of +170 cells/μL during maraviroc therapy versus +144 cells/μL during efavirenz therapy (difference [maraviroc minus efavirenz], +26 cells/μL [95% CI, +7 to +46 cells/μL]; $P = .008$).

Changes in viral tropism. Of the 720 patients with an R5 tropism result at screening, 694 (96.4%) had evaluable baseline tropism data. Of these, 3.5% had a D/M baseline result (maraviroc, 13/344 [3.8%]; efavirenz, 11/350 [3.1%]), indicating low-level CXCR4-using virus around the detection limit of the original Trofile assay. Of the 670 patients with R5 results at both screening and baseline, postbaseline tropism data were available for 644 (96%), of whom 29 (4.5%) had emergence of CXCR4-using virus during receipt of study medication (maraviroc, 20/321; efavirenz, 9/323).

Safety. In the primary analysis, there were 49 (13.6%) discontinuations for adverse events (all cause) during efavirenz therapy and 15 (4.2%) during maraviroc therapy ($P < .001$, Fisher exact test; Table 2). Adverse event–related discontinu-

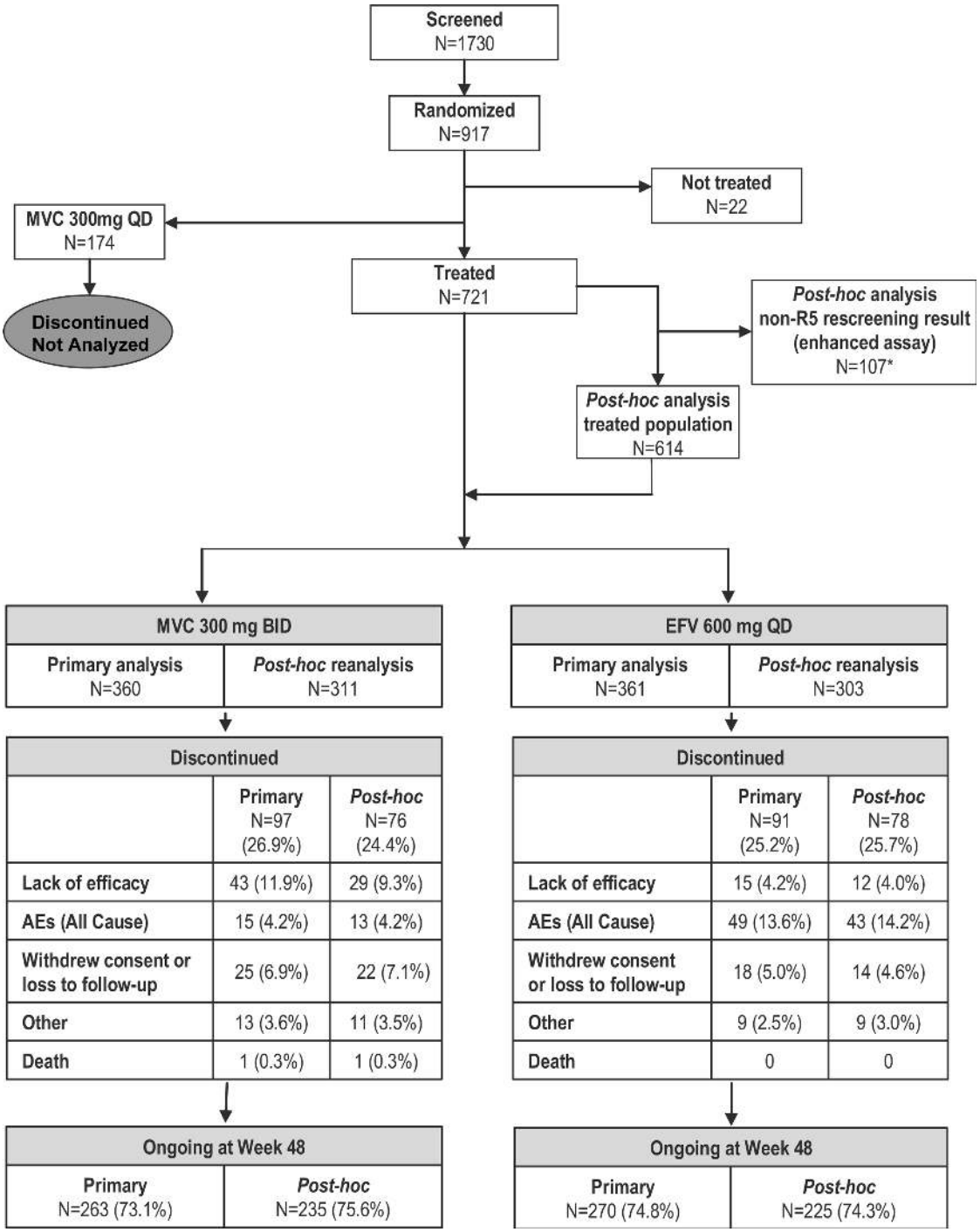

Figure 1. Patient disposition. The asterisk (*) indicates that 1 patient with non-R5 virus at screening was included in the primary population, randomized in error. Only deaths occurring during receipt of study medication are listed. An additional 2 deaths occurred within 28 days of discontinuation of efavirenz plus zidovudine-lamivudine. No death was considered to be related to a study drug. BID, twice a day; AEs, adverse events; EFV, efavirenz; MVC, maraviroc; QD, once a day.

ations occurred earlier during efavirenz therapy, with 59% of all such efavirenz discontinuations through 48 weeks occurring within the first 8 weeks and 78% occurring within 16 weeks, versus 40% and 60%, respectively, during maraviroc therapy.

Adverse events through week 48 are summarized in Table 2, and the most common adverse events are listed in Table 3. Bronchitis and nasopharyngitis were more common (≥2% higher incidence) in the maraviroc arm, whereas diarrhea, vom-

Table 1. Demographic and Baseline Characteristics of Patients in the MERIT Study

Characteristic	Primary analysis		Post hoc reanalysis[a]	
	EFV plus ZDV-3TC (n = 361)	MVC plus ZDV-3TC (n = 360)	EFV plus ZDV-3TC (n = 303)	MVC plus ZDV-3TC (n = 311)
Age, mean (range), years	37.4 (18–77)	36.7 (20–69)	37.3 (18–77)	36.4 (20–69)
Male	259 (71.7)	256 (71.1)	213 (70.3)	220 (70.7)
Race				
White	198 (54.8)	204 (56.7)	161 (53.1)	167 (53.7)
Black	133 (36.8)	123 (34.2)	118 (38.9)	114 (36.7)
Asian	5 (1.4)	6 (1.7)	3 (1.0)	4 (1.3)
Other	25 (6.9)	27 (7.5)	21 (6.9)	26 (8.4)
$CD4^+$ cell count, median (range), cells/μL	254 (8–1053)	241 (5–1422)	254 (39–1053)	236 (5–1016)
HIV-1 RNA level, mean ± SD, $\log_{10}$ copies/mL	4.88 ± 0.70	4.86 ± 0.64	4.85 ± 0.62	4.88 ± 0.68

NOTE. Data are no. (%) of patients, unless otherwise specified. All patients who received at least 1 dose of study medication are included. 3TC, lamivudine; EFV, efavirenz; MVC, maraviroc; SD, standard deviation; ZDV, zidovudine.

[a] Includes only those patients with an R5 screening result by the enhanced Trofile assay.

iting, dizziness, abnormal dreams, cough, and rash were more common in the efavirenz arm.

Twice as many patients experienced category C events during efavirenz therapy (3.3% vs 1.7%) (Table 2). Malignancies were also twice as common in the efavirenz arm (7 vs 3 events, affecting 7 [1.9%] vs 2 [0.6%] patients). The overall incidence of grade 3 or 4 increases in transaminase levels was low, and the incidences were similar in both treatment groups (Table 2). One patient in the discontinued once-daily maraviroc arm experienced potentially life-threatening hepatotoxicity, which has been presented in more detail elsewhere [15]. The data implicated isoniazid and/or cotrimoxazole toxicity, but maraviroc could not be ruled out as a potential contributor.

Post hoc reanalysis. When the interim analysis was repeated post hoc for only patients with an R5 screening tropism result by the enhanced Trofile assay, the relevant CI bounds for the differences in end points between the once-daily maraviroc group and the efavirenz group no longer fell outside the noninferiority thresholds defined for the full prospective data set. The mean time-averaged differences for once-daily maraviroc (n = 56) and efavirenz (n = 58) were −2.28 and −2.38 $\log_{10}$ copies/mL (difference, 0.10 $\log_{10}$ copies/mL [97.5% CI upper bound, 0.39 $\log_{10}$ copies/mL), and the proportions of patients with <400 RNA copies/mL were 82.1% versus 86.2% (adjusted difference, −4% [97.5% CI lower bound, −19%]).

Of the 721 patients included in the primary 48-week analysis, 107 (15%) had a D/M virus screening result by the enhanced Trofile assay, including 1 patient originally randomized to maraviroc in error. These patients were excluded from the reanalysis, leaving 614 patients (maraviroc, 311; efavirenz, 303) with confirmed R5 virus. Exclusion of the 107 patients did not alter the balance of characteristics between groups (Table 1) but reduced the rate of discontinuations of maraviroc for lack of efficacy to 9.3% (from 11.9% in the primary analysis) (Figure 1). There was no notable effect on the rate of efavirenz discontinuation (4.0% [post hoc] vs 4.2% [primary]). Moreover, the lower bound of the 97.5% CI was above −10% for both coprimary end points: stratification-adjusted differences between treatment groups were 0.6% (97.5% CI lower bound, −6.4%) for the <400 copies/mL end point and −0.2% (97.5% CI lower bound, −7.4%) for the <50 copies/mL end point (Figure 2*B*). Maraviroc response rates within the randomization subgroups were also higher than those in the primary analysis, particularly for patients with high baseline HIV-1 RNA levels (Figure 2*C*). As with the primary analysis, mean changes in $CD4^+$ cell count from baseline favored the maraviroc arm (difference [maraviroc minus efavirenz], +30 cells/μL [95% CI, +10 to +51 cells/μL]; P = .004).

Viral tropism and resistance in the post hoc reanalysis. Most patients (102 of 106) reclassified by the enhanced assay as having CXCR4-using virus at screening had subsequent tropism data collected during the study (Table 4). Within this subgroup, virologic suppression rates at week 48 were lower for maraviroc (21 [46%] of 46) (Figure 3) than for efavirenz (42 [75%] of 56). The enhanced assay identified CXCR4-using virus at screening in 11 (48%) of 23 patients who had a change in tropism result with the original Trofile assay from R5 at screening to CXCR4 using at baseline (Table 4). Among 29 patients who by the original assay had R5 virus at both screening and baseline but had CXCR4-using virus during treatment, the enhanced assay identified 16 patients (55%) with CXCR4-using virus at screening. An additional 75 patients were reclassified as having CXCR4-using virus at screening from among 615 patients who showed no evidence of CXCR4-using virus at any time during the study according to the original Trofile results.

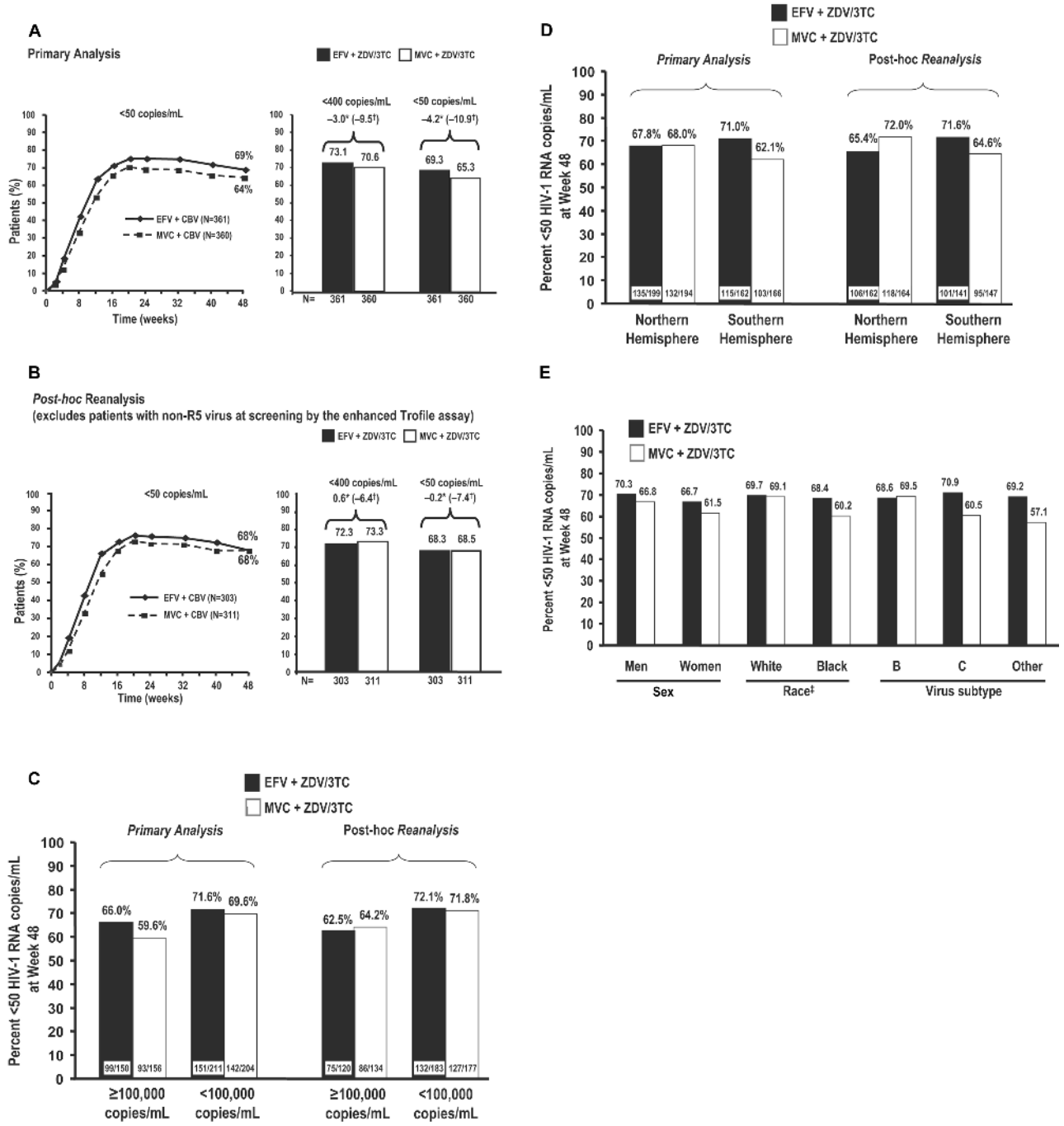

Figure 2. Proportions of patients with <50 human immunodeficiency virus type 1 (HIV-1) RNA copies/mL by study visit and randomization strata–adjusted week 48 treatment differences for the coprimary end points (proportions of patients with <400 and <50 copies/mL at week 48) in the primary analysis (*A*) and in the post hoc reanalysis (*B*), which excluded patients with non-R5 virus at screening by the enhanced Trofile assay, and proportions of patients with <50 HIV-1 RNA copies/mL at week 48 by baseline HIV-1 RNA level (primary and post hoc reanalyses) (*C*), by geographic location (primary and post hoc reanalyses) (*D*), and by other baseline subgroups (primary analysis only) (*E*). *Difference (adjusted for randomization strata). †Lower bound of 1-sided 97.5% confidence interval. ‡Other races combined (nonwhite, nonblack) represented less than 9% of the total population and are not included. 3TC, lamivudine; EFV, efavirenz; MVC, maraviroc; ZDV, zidovudine.

Table 2. Adverse Events (All Cause, Primary 48-Week Analysis)

Parameter	EFV plus ZDV-3TC (n = 361)	MVC plus ZDV-3TC (n = 360)
Patients with adverse events	340 (94.2)	331 (91.9)
Patients with grade 3 adverse events	66 (18.3)	51 (14.2)
Patients with grade 4 adverse events	24 (6.6)	22 (6.1)
Patients with serious adverse events[a]	46 (12.7)	41 (11.3)
Patients with category C events	12 (3.3)	6 (1.7)
Tuberculosis[b]	8	1
Herpes simplex[b]	1	1
Lobar pneumonia or LRTI[b]	0	2
Pneumocystis jirovecl[b]	0	1
Hodgkin disease[b]	2	0
NHL or diffuse large B cell lymphoma[b]	1	1
Kaposi sarcoma[b]	1	0
Malignancies	7 events[c] in 7 patients	3 events[d] in 2 patients
Deaths[a,e]	1	1
Grade 3–4 elevation in transaminase levels		
Patients with grade 3 ALT elevation	11 (3.1)	9 (2.5)
Patients with grade 4 ALT elevation	2 (0.6)	2 (0.6)
Patients with grade 3 AST elevation	11 (3.1)	7 (2.0)
Patients with grade 4 AST elevation	2 (0.6)	5 (1.4)
Adverse events causing discontinuation[f]		
CNS[g]	16 (4.4)	3 (0.8)
Rash or hypersensitivity	8 (2.2)	0 (0)
Elevated transaminase or GGT level	5 (1.4)	5 (1.4)
Rash and elevated transaminase level	1 (0.3)	0 (0)
Rash and CNS	1 (0.3)	0 (0)
Tuberculosis	7 (1.9)	1 (0.3)
Hepatitis C (treatment emergent)	0 (0)	2 (0.6)
Anemia or pancytopenia	3 (0.8)	0 (0)
Lymphoma or malignancy	1 (0.3)	1 (0.3)
Malignancy and anemia	1 (0.3)	0 (0)
Malignancy, pancytopenia, and CNS	1 (0.3)	0 (0)
Other[h]	5 (1.4)	3 (0.8)
Total	49 (13.6)	15 (4.2)[i]

NOTE. Data are no. (%) of patients, unless otherwise indicated. 3TC, lamivudine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNS, central nervous system; EFV, efavirenz; GGT, γ glutamyl transpeptidase; LRTI, lower respiratory tract infection; MVC, maraviroc; NHL, non-Hodgkin lymphoma; ZDV, zidovudine.

[a] Based on all data through 21 June 2007.

[b] No. of events.

[c] Basal cell carcinoma, $n = 2$; Castleman disease, $n = 1$; Hodgkin disease, $n = 2$; Kaposi sarcoma, $n = 1$; NHL, $n = 1$.

[d] Diffuse large B cell lymphoma, $n = 1$; metastasis to bone, $n = 1$; skin cancer, $n = 1$.

[e] Deaths reported up to 28 days after stopping drug; 1 additional death occurred in the efavirenz arm within 28 days. No death was considered to be related to a study drug. Causes of death were as follows: for maraviroc, pulmonary embolism; for efavirenz, Castleman disease and NHL.

[f] In any individual, other adverse events may have occurred together with the key adverse events listed.

[g] Anxiety with or without panic attacks; insomnia; sleep disorder; suicidal ideation or attempt; major depression; headache; nightmare; dizziness; hangover, sluggishness, or emotional distress; confusion; restlessness; disturbed attention; somnolence; double vision; vertigo; abnormal dreams; or hallucinations.

[h] For efavirenz, gynecomastia, myocardial infarction, renal failure, hepatitis, and relapse substance abuse; for maraviroc, myositis, syncope, and nausea, vomiting, or pyrexia.

[i] $P < .001$ vs the efavirenz group (Fisher exact test).

Full virologic data sets were obtained for 29 maraviroc-treated and 13 efavirenz-treated patients who experienced virologic failure by the TLOVR algorithm (<50 copies/mL threshold). As was found for treatment-experienced patients, the mechanisms of resistance observed for maraviroc included emergence of CXCR4-using virus (9/29 [31%]) and selection of CCR5-tropic virus with resistance to maraviroc (4/29 [14%]). Five patients experienced treatment failure with only lamivudine-resistant virus. In addition, failure was observed without any resistance detected for 11 (38%) of these 29 patients, 9 (82%) of whom had at least 1 episode of poor adherence to therapy with at least 1 episode of undetectable maraviroc in plasma at a study visit and/or intermittent viral load response. In contrast, in the case of failure with efavirenz, the majority of patients showed efavirenz resistance (9/13 [69%]), 4 of whom had resistance to lamivudine and 1 of whom had resistance to zidovudine. Failure with lamivudine resistance alone was observed in 1 patient, and a total of 3 (23%) of 13 patients experienced failure without any detected resistance. In addition, 5 patients in the efavirenz group who discontinued therapy because of adverse events developed new efavirenz resistance mutations while not receiving treatment during follow-up, whereas there was no evidence of nucleoside reverse-transcriptase inhibitor mutations or emergence of CXCR4-using virus during follow-up of patients discontinuing maraviroc because of adverse events.

DISCUSSION

Initiated in 2004, MERIT used a then standard-of-care zidovudine-lamivudine backbone, and response rates in both arms were somewhat lower than those in recent treatment-naive studies that used more tolerable tenofovir-containing backbones [16, 17]. However, allowing for the limitations of cross-study comparisons and differences in regimen potencies, response rates in MERIT were broadly comparable to those observed in other treatment-naive studies using backbones without tenofovir [18–21] and were similar to those observed in previous studies of efavirenz with zidovudine-lamivudine [22–24].

In the primary 48-week analysis, twice-daily maraviroc plus zidovudine-lamivudine did not meet the criteria for noninferiority to once-daily efavirenz plus zidovudine-lamivudine at <50 copies/mL, because of more discontinuations for lack of efficacy in the maraviroc arm. This was in part due to the

Table 3. Most Common Adverse Events over 48 Weeks (All Cause, Unadjusted for Exposure)

The table is available in its entirety in the online version of the *Journal of Infectious Diseases*.

Table 4. Reclassification of MERIT Patients by the enhanced Trofile Assay among Groups Defined by the Original Trofile Assay Result at Screening, Baseline, and During Receipt of Study Medication

Original Trofile assay result (treatment groups combined)			Reclassified by enhanced Trofile assay as D/M at screening, proportion (%)		
Screening→baseline	D/M after baseline[a]	No. of patients	All	MVC	EFV
R5→D/M	…	23	11/23 (47.8)	7/13 (53.8)	4/10 (40.0)
R5→R5	Yes	29	16/29 (55.2)	10/20 (50.0)	6/9 (66.7)
R5→R5	No	615	75/615 (12.2)	29/301 (9.6)	46/314 (14.6)

NOTE. The table excludes patients with a D/M or nonreportable tropism result by the original Trofile assay at screening and patients with an R5 result at screening and baseline but without postbaseline tropism data. D/M, dual or mixed tropic.

[a] At least 1 postbaseline D/M result by the original Trofile assay.

inclusion of patients with CXCR4-using virus populations present below the detection limit of the original screening tropism assay. When the screening samples were blindly retested with the current, more sensitive assay, 15% of patients were found to have been carrying CXCR4-using virus at screening. Post hoc exclusion of these patients produced a data set with baseline characteristics similar to those of the full population but with fewer maraviroc discontinuations due to lack of efficacy. When the prespecified analyses were applied to this post hoc data set, the CI bounds for the differences in end points between the treatment groups no longer fell outside the noninferiority thresholds.

In the primary analysis, virologic response rates for maraviroc were slightly lower in patients from the Southern Hemisphere, in black patients, and in patients with non–subtype B infections than in other patient groups. The majority of black patients and patients with non-B virus came from the Southern Hemisphere, where most patients (68%) were enrolled in South Africa; thus, these observations may be linked and may represent a regional difference in physicians' management of patients within the study. Differences in response rates in black patients appear to have been driven by more black patients receiving maraviroc (13%) than efavirenz (4.5%) defaulting (lost to follow-up or withdrawal of consent). Notably, rates of discontinuation for lack of efficacy among black patients were similar between treatment groups. Increases from baseline in $CD4^+$ cell count were significantly greater for maraviroc than for efavirenz.

In the post hoc reanalysis, response rates were similar between the treatment groups within each screening viral load stratum. Response rates were higher for maraviroc than for efavirenz in the Northern Hemisphere but were higher for efavirenz than for maraviroc in the Southern Hemisphere. These results appeared to be driven by higher adverse event–related discontinuation rates for efavirenz in the Northern Hemisphere and by more black patients receiving maraviroc than efavirenz defaulting in the Southern Hemisphere.

Although performed in a subpopulation similar to the primary population and with blinded tropism reassessment, the post hoc reanalysis was retrospective and does not supersede the MERIT primary efficacy outcome. The results of the reanalysis are, however, supported by similar findings of an analogous reanalysis of AIDS Clinical Trials Group 5211, a study of the investigational CCR5 antagonist vicriviroc that also used the original Trofile assay for screening [25]. In the present reanalysis, the detection of minority CXCR4-using viruses was associated with an increased risk of virologic failure during maraviroc therapy, similar to the observation of an increased risk of failure during treatment with other agents in the presence of minority resistant variants [26].

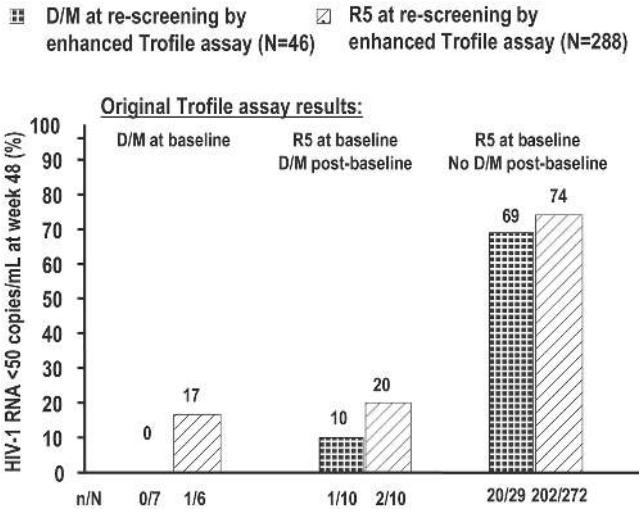

Figure 3. Proportions of patients with virologic suppression (human immunodeficiency virus type 1 [HIV-1] RNA level of <50 copies/mL) in the maraviroc group by enhanced Trofile assay screening tropism result, according to groups defined by the original Trofile assay result at screening, baseline, and during receipt of study medication. All patients with an R5 screening result by the original Trofile assay are included. D/M, dual or mixed tropic; n/N, number with <50 HIV-1 RNA copies/mL at week 48 per the total number in the specified subgroup.

Maraviroc was associated with significantly fewer adverse event–related discontinuations than efavirenz and with fewer malignancies and category C events, although these differences were not statistically significant. There were no significant differences between treatment groups in the incidence of elevations in transaminase levels, and there were no unexpected safety findings.

Patients discontinuing therapy because of adverse events in the efavirenz group had a slightly lower rate of virologic suppression than did those in the maraviroc group (31% [15/49] vs 40% [6/15], respectively), and efavirenz resistance mutations emerged in some individuals after drug withdrawal. These observations are consistent with prior observations of nonnucleoside reverse-transcriptase inhibitor (NNRTI) resistance emerging after withdrawal of NNRTI-based regimens [27] and suggest that adverse event–related nonadherence or other nonvirologic discontinuation of an NNRTI may risk compromising its subsequent activity, as well as that of other agents in this class. Follow-up information is available for a subset of patients who discontinued therapy. Among those from the original analysis set for whom data were available for $\geqslant$22 weeks after discontinuation, virologic suppression rates were higher in patients who received maraviroc before discontinuation (64% [27/42] for maraviroc vs 55% [18/33] for efavirenz). These data suggest that, as with efavirenz-based HAART, some patients who discontinue an initial maraviroc regimen for any reason can undergo successful salvage therapy with a subsequent regimen. Moreover, the results of the resistance analyses in this study are similar to those of treatment-naive studies involving vicriviroc [28] and aplaviroc [29, 30].

These findings suggest that maraviroc may address some of the challenges associated with current antiretroviral agents and could benefit a significant proportion of treatment-naive patients. Data from across the phase 2b/3 clinical program, which involve >2000 patients exposed to maraviroc over periods in excess of 96 weeks [4, 9, 31], indicate that maraviroc has a tolerability profile similar to that of placebo. Furthermore, previously presented lipid analyses in MERIT have suggested that maraviroc may offer some advantages compared with efavirenz in terms of effects on cholesterol and triglycerides—for example, in patients with elevated levels of low-density lipoprotein cholesterol before treatment, who may be at increased long-term risk for cardiovascular disease [32]. The tolerability profile of maraviroc and the high prevalence of R5 HIV among treatment-naive patients may be particularly relevant given the recent revised interest in the potential benefits of earlier initiation of ART, when $CD4^+$ cell counts are still fairly high (>500 cells/μL) [33].

In conclusion, the primary 48-week analysis of MERIT showed that treatment-naive patients with R5 HIV-1 infection receiving 300 mg of maraviroc twice a day with zidovudine and lamivudine displayed better $CD4^+$ cell count increases and a lower rate of adverse event–related discontinuations—but a lower rate of virologic response—than did similar patients receiving 600 mg of efavirenz once a day with the same nucleosides. Subsequent reanalysis showed that this lower response rate for maraviroc than for efavirenz was due to the presence of CXCR4-using virus in a subset of patients not detected by the original Trofile assay. Repeating the analyses in the subset of MERIT patients eligible for study entry according to a newer, more sensitive screening assay resulted in similar 48-week response rates between treatments.

POTENTIAL CONFLICTS OF INTEREST

D.A.C. has received consultancy, honoraria and grant support from BMS, Gilead, GSK, Pfizer, Tibotec, Johnson & Johnson, Boehringer-Ingelheim, Merck, Abbott, Schering-Plough, and Tobira. J.H. is an employee of Pfizer and holds stock and stock options in Pfizer. J.G. is an employee of Pfizer and holds stock and stock options in Pfizer. M.T. is an employee of Pfizer and holds stock and stock options in Pfizer. M.S. has received consultancy fees from Avexa, Boehringer-Ingelheim, Bristol Myers Squibb, Gilead, GlaxoSmithKline, Merck Sharp and Dohme, Monogram Biosciences, Pain Therapeutics, Panacos, Pfizer, Progenics, Roche, and Tibotec; he has also received grant support from Achillion Pharmaceuticals, Boehringer-Ingelheim, Gilead Sciences, GlaxoSmithKline, Merck Sharp and Dohme, Panacos, Pfizer, Progenics, and Tibotec. E.D. has received research support from Abbott Laboratories, Achillion, Avexa, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Hoffman LaRoche Laboratories, Merck, Pfizer, Schering-Plough, Taimed, Tobira, Tibotec, and Vertex; he has also received consultancy fees from Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Tibotec, and Vertex Pharmaceuticals, in addition to participating in speakers' bureaus for Gilead Sciences, Merck, Tibotec, and Virco. N.C. has received consultancy fees from Gilead, Pfizer, Abbott, and Merck Sharp and Dohme. S.W. is a consultant on advisory boards, speakers' bureaus, and has participated in the conduct of clinical trials with Boehringer-Ingelheim, Roche, Abbott, Bristol-Myers Squibb, GlaxoSmithKline, Gilead, Tibotec, Merck, and Pfizer. N.T. is an employee of Pfizer and holds stock and stock options in Pfizer. E.C. is an employee of Monogram Biosciences. J.R. is an employee of Monogram Biosciences. G.R.-T. is employed as the Head, Department of Research in Infectious Diseases at the National Institute of Respiratory Diseases, Mexico. M.W. is an employee of Pfizer and holds stock and stock options in Pfizer. E.V.D.R. is an employee of Pfizer and holds stock and stock options in Pfizer. P.I. has not received consultancy fees or grant support from any pharmaceutical company and has no conflict of interest for this article. L.M. declares no conflict of interest. H.M. has received con-

sultancy fees from Abbott Laboratories. A.H. received consultancy fee from Tibotec. F.H. is an employee of Pfizer and holds stock and stock options in Pfizer. J.S. is an employee of Pfizer and holds stock and stock options in Pfizer. H.M. was, at the time of these analyses, an employee of Pfizer with stock and stock options in Pfizer.

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