ORIGINAL ARTICLE

# Subgroup Analyses of Maraviroc in Previously Treated R5 HIV-1 Infection

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## ABSTRACT

### BACKGROUND

We conducted subanalyses of the combined results of the Maraviroc versus Optimized Therapy in Viremic Antiretroviral Treatment-Experienced Patients (MOTIVATE) 1 and MOTIVATE 2 studies to better characterize the efficacy and safety of maraviroc in key subgroups of patients.

### METHODS

We analyzed pooled data from week 48 from the two studies according to sex, race or ethnic group, clade, CC chemokine receptor 5 (CCR5) delta32 genotype, viral load at the time of screening, the use or nonuse of enfuvirtide in optimized background therapy (OBT), the baseline CD4 cell count, the number of active antiretroviral drugs coadministered, the first use of selected background agents, and tropism at baseline. Changes in viral tropism and the CD4 count at treatment failure were evaluated. Data on aminotransferase levels in patients coinfected with hepatitis B virus (HBV) or hepatitis C virus (HCV) were also analyzed.

### RESULTS

A treatment benefit of maraviroc plus OBT over placebo plus OBT was shown in all subgroups, including patients with a low CD4 cell count at baseline, those with a high viral load at screening, and those who had not received active agents in OBT. Analyses of the virologic response according to the first use of selected background drugs showed the additional benefit of adding a potent new drug to maraviroc at the initiation of maraviroc therapy. More patients in whom maraviroc failed had a virus binding to the CXC chemokine receptor 4 (CXCR4) at failure, but there was no evidence of a decrease in the CD4 cell count at failure in such patients as compared with those in whom placebo failed. Subanalyses involving patients coinfected with HBV or HCV revealed no evidence of excess hepatotoxic effects as compared with baseline.

### CONCLUSIONS

Subanalyses of pooled data from week 48 indicate that maraviroc provides a valuable treatment option for a wide spectrum of patients with R5 HIV-1 infection who have been treated previously. (ClinicalTrials.gov numbers, NCT00098306 and NCT00098722.)

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The CC chemokine receptor 5 (CCR5) antagonist maraviroc has shown potent antiviral activity in vitro and in vivo against the R5 human immunodeficiency virus type 1 (HIV-1).[1,2] As reported by Gulick et al.[3] elsewhere in this issue, treatment with maraviroc plus optimized background therapy was associated with significantly greater virologic and immunologic efficacy and had a similar safety profile, as compared with placebo plus optimized background therapy, in the Maraviroc versus Optimized Therapy in Viremic Antiretroviral Treatment-Experienced Patients (MOTIVATE) 1 and MOTIVATE 2 studies at 48 weeks.

Subgroup analyses of data from recent trials evaluating new drugs in patients who have received previous treatment for HIV-1 infection have contributed important information.[4-6] For example, optimal responses with enfuvirtide are achieved when at least two other active drugs are added.[7] The addition of enfuvirtide to a regimen containing raltegravir resulted in a higher response rate than raltegravir regimens without enfuvirtide.[8] Similar results were achieved with the addition of enfuvirtide, used for the first time, to a regimen containing darunavir and ritonavir.[4]

Although virus binding to the CX chemokine receptor 4 (CXCR4) can be detected in more than 50% of persons with severe immunodeficiency,[9] a causal relationship between the emergence of this virus and a decrease in the CD4 cell count has not been established. The demonstration of emergent virus binding to CXCR4 (resulting from the outgrowth of preexisting, low levels of variants binding to CXCR4) as an important mechanism of viral escape from CCR5 antagonists[10,11] has increased concern that virologic failure after treatment with a CCR5 antagonist may have deleterious effects on CD4 cell counts.

Our analysis of the overall population in the MOTIVATE 1 and MOTIVATE 2 studies did not show any significant differences in severe hepatotoxic effects between maraviroc and placebo.[3] However, experimental data show that CCR5 deficiency can negatively influence the course of hepatitis in mice.[12,13] Furthermore, conflicting data on the effect of the CCR5 delta32 mutation on the clinical course of hepatitis C virus (HCV) infection have been published.[14-16] Data on the use of CCR5 antagonists in HIV-positive patients with hepatitis B virus (HBV) or HCV coinfection are currently very limited, in spite of the size of this subgroup of patients in clinical practice.[17,18]

This article presents the results of several subgroup analyses of pooled data from week 48 in the MOTIVATE 1 and MOTIVATE 2 studies in order to address these issues.

## METHODS

The design, conduct, monitoring, and statistical analyses of the MOTIVATE 1 and MOTIVATE 2 studies are described in the article by Gulick et al.[3]

### STUDY DESIGN

We conducted subgroup analyses of data from the combined MOTIVATE 1 and MOTIVATE 2 study populations. A pooled analysis was performed because the studies had identical designs, with similar baseline characteristics for each study population. When the studies were designed, the change in viral load from baseline (on the $\log_{10}$ scale) was chosen as the primary end point, since this was the most commonly used end point at the time in this population.[7,19] However, with the advent of potent, new antiretroviral agents that are active against drug-resistant HIV-1, the proportion of patients in whom the HIV-1 RNA level becomes undetectable (<50 copies per milliliter) is a more clinically relevant end point, even in patients with clinically significant viral resistance at baseline, and this end point is presented here.

All 1049 patients who underwent randomization and received a study drug were included in the analyses of the proportion of patients in whom an HIV-1 RNA level of less than 50 copies per milliliter was achieved. Patients who discontinued the study drug for any reason were included in the analysis as patients who did not have a response. To calculate the change in the CD4 cell count from baseline, the last-observation-carried-forward approach was used to impute missing values.

Preplanned subgroup analyses included an evaluation of treatment efficacy according to sex; race or ethnic group; clade (B or non-B); CCR5 delta32 genotype; viral load at screening (<100,000 or ≥100,000 copies per milliliter); baseline value of the CD4 cell count, which was calculated as the mean of two assessments made before the receipt of the study drug (i.e., <50, 50 to 100, 101 to 200, 201 to 350, and >350 cells per cubic millimeter); use or nonuse of enfuvirtide in the optimized background therapy; and number of potentially active drugs in the optimized background therapy according to baseline genotypic, phenotypic, and overall susceptibility scores, which were cal-

culated as described by Gulick et al.[3] The change in the CD4 cell count from baseline was analyzed according to the viral load at the time of screening and the baseline CD4 cell count. The subgroup categories were also prespecified.

Post hoc analyses of the efficacy of maraviroc in combination with optimized background therapy containing enfuvirtide, lopinavir–ritonavir, or tipranavir were conducted on the basis of first use of the selected drug. A post hoc analysis of the virologic response according to tropism at baseline was also performed.

Data on hepatic safety, including maximum and last on-treatment liver-enzyme values, were analyzed for patients who were coinfected with HBV or HCV; coinfection was defined as hepatitis B surface-antigen positivity or HCV RNA positivity at screening. Liver-enzyme testing was performed at screening, at baseline, at week 2, at week 4, every 4 weeks through week 24, and every 8 weeks through week 48. Elevations were graded according to the Division of AIDS Table for Grading Severity of Adult Adverse Experiences.[20]

Coreceptor tropism was determined with the use of a validated phenotypic tropism assay[21] (Trofile, Monogram Biosciences, South San Francisco) at screening, at baseline, and at all study visits after week 4 in patients with an HIV-1 RNA level of more than 500 copies per milliliter. This assay has a reported 100% sensitivity for detecting variants binding to CXCR4 occurring at the 10% level and 85% sensitivity for detecting variants occurring at the 5% level.[21] The results of the tropism assay at the time of virologic failure (defined by Gulick et al.[3]) and changes in the CD4 cell count from baseline at this time point were evaluated.

### STATISTICAL ANALYSIS

The individual studies were powered to show a difference in the overall population, not in separate subgroups. Since these studies were for drug-registration purposes, only hypothesis tests that were described in the plan for statistical analysis, which was finalized before the databases were unblinded, were included in the study reports. For subgroups, summary tables only were prespecified. Post hoc analyses were performed as previously described.[22]

Heterogeneity among covariate levels in each subgroup was assessed. For each subgroup, a logistic-regression model was fitted. This model included the treatment, the two randomization strata (the HIV-1 RNA level at screening [<100,000 copies per milliliter or ≥100,000 copies per milliliter] and the use or nonuse of enfuvirtide in optimized background therapy), the relevant subgroup, and the interaction between treatment and subgroup. The interaction term was assessed for significance at the 5% level. If it was significant, it was concluded that there was evidence of a different treatment effect across the levels of the subgroup. For each covariate level in a subgroup, a point estimate of the odds ratio and its associated confidence interval were presented in a forest plot. The change in the CD4 cell count from baseline according to subgroup was analyzed with the use of analysis of covariance in an analogous manner, with least-square means and associated confidence intervals presented in a forest plot. All reported P values are two-sided and have not been adjusted for multiple testing.

## RESULTS

### STUDY POPULATION

The baseline characteristics of the patients were similar across all study groups (Table 1). The majority of patients were male (89%) and white (84%), and 14% were black. At the time of screening, more than 40% of patients had an HIV-1 RNA level of 100,000 copies per milliliter or greater and approximately 20% had baseline CD4 cell counts that were less than 50 cells per cubic millimeter. Overall susceptibility scores indicated that 17% of patients in the placebo group and 13% in the maraviroc groups had no potentially active drugs in their optimized background therapy. A total of 82% of patients were taking antiretroviral drugs at the time of study entry; 18% had not taken antiretroviral drugs within 7 days before study entry, which may have led to an underestimation of the degree of viral resistance in these patients. A total of 8% of patients were heterozygous for the CCR5 delta32 genotype, and 94% were infected with clade B HIV-1.

### VIROLOGIC EFFICACY IN SUBGROUPS

Table 2 summarizes the associations of the subgroup variables with an HIV-1 RNA level of less than 50 copies per milliliter at week 48 in univariate and multivariate analyses of data from the whole study population. Race or ethnic group; viral load at the time of screening; baseline CD4 cell

**Table 1. Baseline Characteristics of the Patients in the Subgroup Analysis.***

| Characteristic | Placebo plus Optimized Background Therapy (N=209) | Maraviroc Once Daily plus Optimized Background Therapy (N=414) | Maraviroc Twice Daily plus Optimized Background Therapy (N=426) |
|---|---|---|---|
| | | *no. (%)* | |
| Screening HIV-1 RNA ≥100,000 $\log_{10}$ copies/ml | 84 (40) | 175 (42) | 179 (42) |
| Baseline CD4 count <50 cells/$mm^3$† | 38 (18) | 84 (20) | 85 (20) |
| Genotypic susceptibility score | | | |
| 0 | 50 (24) | 92 (22) | 102 (24) |
| 1 | 54 (26) | 145 (35) | 138 (32) |
| 2 | 41 (20) | 64 (15) | 80 (19) |
| ≥3 | 59 (28) | 108 (26) | 104 (24) |
| Missing data | 5 (2) | 5 (1) | 2 (<1) |
| Phenotypic susceptibility score§ | | | |
| 0 | 29 (14) | 45 (11) | 50 (12) |
| 1 | 38 (18) | 116 (28) | 115 (27) |
| 2 | 57 (27) | 95 (23) | 106 (25) |
| ≥3 | 80 (38) | 152 (37) | 151 (35) |
| Missing data | 5 (2) | 6 (1) | 4 (<1) |
| Overall susceptibility score | | | |
| 0 | 35 (17) | 52 (13) | 57 (13) |
| 1 | 43 (21) | 134 (32) | 136 (32) |
| 2 | 59 (28) | 89 (21) | 103 (24) |
| ≥3 | 67 (32) | 132 (32) | 126 (30) |
| Missing data | 5 (2) | 7 (2) | 4 (<1) |
| Optimized background therapy | | | |
| Enfuvirtide | 90 (43) | 169 (41) | 182 (43) |
| Tipranavir | 29 (14) | 67 (16) | 64 (15) |
| Lopinavir | 60 (29) | 124 (30) | 155 (36) |
| Protease inhibitor,‡ delavirdine, or both§ | 171 (82) | 320 (77) | 335 (79) |

* Data for all patients who received at least one dose of study treatment are included, except where indicated.
† The baseline value for each patient was calculated as the mean of up to two assessments made before receipt of the study drug (at screening and the baseline visit). Data for patients who had valid values at baseline and during treatment are included. Data were missing for one patient in the placebo group and one patient in the group receiving maraviroc once daily.
‡ This group of protease inhibitors does not include tipranavir.
§ The dose of maraviroc was 150 mg (once daily or twice daily) for patients who received a protease inhibitor (excluding tipranavir), delavirdine, or both as part of their optimized background therapy; otherwise, the dose of maraviroc was 300 mg (once or twice daily).

count; scores for genotypic, phenotypic, and overall susceptibility; tropism at baseline; and the first use of enfuvirtide, lopinavir–ritonavir, or tipranavir were associated with the virologic response in the univariate analysis. Race or ethnic group, clade, viral load at the time of screening, baseline CD4 cell count, overall susceptibility score, and first use of enfuvirtide showed evidence of association in the multivariate analysis.

In all 14 treatment subgroups analyzed, there was a greater likelihood of a complete virologic response (i.e., an HIV-1 RNA level of <50 copies

**Table 2. Association Between Baseline Variables and Virologic Response at Week 48.***

| Variable | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| | P Value | Odds Ratio (95% CI) | P Value | Odds Ratio (95% CI) |
| Sex | 0.94 | 1.02 (0.67–1.53) | 0.42 | 1.24 (0.74–2.06) |
| Race | <0.001 | 2.54 (1.66–3.91) | <0.001 | 3.27 (1.96–5.47) |
| Clade | 0.54 | 0.83 (0.46–1.50) | 0.004 | 0.33 (0.14–0.77) |
| CCR5 delta32 genotype | 0.08 | 0.64 (0.39–1.05) | 0.20 | 0.68 (0.39–1.17) |
| Viral load at screening | <0.001 | 2.64 (2.01–3.48) | <0.001 | 2.13 (1.53–2.97) |
| Enfuvirtide in optimized background therapy (stratification factor)† | 0.12 | 1.24 (0.95–1.62) | NA | NA |
| CD4 cell count | <0.001 | 0.18 (0.11–0.28) | <0.001 | 0.25 (0.15–0.42) |
| Genotypic susceptibility score | <0.001 | 0.40 (0.30–0.53) | 0.38 | 0.73 (0.48–1.10) |
| Phenotypic susceptibility score | <0.001 | 0.39 (0.30–0.53) | 0.57 | 1.22 (0.62–2.41) |
| Overall susceptibility score | <0.001 | 0.37 (0.28–0.49) | 0.04 | 0.45 (0.22–0.90) |
| Tropism | 0.02 | 1.77 (1.10–2.83) | 0.10 | 1.60 (0.93–2.76) |
| Optimized background therapy containing enfuvirtide (first use) | <0.001 | 3.93 (2.48–6.22) | <0.001 | 2.60 (1.53–4.41) |
| Optimized background therapy containing lopinavir–ritonavir (first use) | 0.002 | 2.88 (1.58–5.25) | 0.44 | 1.58 (0.77–3.25) |
| Optimized background therapy containing tipranavir (first use) | <0.001 | 1.96 (0.98–3.93) | 0.52 | 1.14 (0.52–2.52) |

* A complete virologic response is defined as an HIV-1 RNA level of less than 50 copies per milliliter. Univariate and multivariate logistic-regression analyses were carried out for all subgroups. The univariate analysis fitted the subgroup in a logistic-regression model adjusting for all other terms in the model, which contained the treatment and randomization strata covariates. The multivariate analysis fitted the subgroup in a logistic-regression model adjusting for all other terms in the model, which contained the treatment and randomization strata covariates and all covariates shown in the table. Odds ratios are for male versus female, white versus black, clade B versus non-B, CCR5 delta32 genotype wt/wt versus delta32/wt, viral load at screening of less than 100,000 copies per milliliter versus 100,000 copies per milliliter or more, the use or nonuse of enfuvirtide in optimized background therapy (stratification factor), baseline CD4 cell count of less than 50 versus 50 or more, genotypic, phenotypic, and overall susceptibility scores of 0 to 1 versus more than 1, tropism at baseline (R5 versus non-R5), and optimized background therapy containing enfuvirtide, lopinavir–ritonavir, or tipranavir used for the first time versus these drugs used but not for the first time. Race was determined by the physicians. NA denotes not applicable, and wt wild type.

† Enfuvirtide is not included in the multivariate analysis since the variable for enfuvirtide in optimized background therapy is included in the data for optimized background therapy containing enfuviritide (first use).

per milliliter) at week 48 in the maraviroc treatment groups than in the placebo group (Fig. 1 and 2).

All subgroups were analyzed to assess whether the beneficial effect of maraviroc on virologic suppression (i.e., an HIV-1 RNA level of <50 copies per milliliter) seen overall may have varied among certain patient subgroups. Five of these subgroups showed evidence of heterogeneity, with significant tests for interaction; these were race or ethnic group (P<0.001), clade (P<0.001), phenotypic susceptibility score (P=0.02), overall susceptibility score (P=0.007), and the first use of tipranavir (P<0.001). For all covariate levels in these subgroups, patients receiving maraviroc were more likely to have a complete virologic response than were patients receiving optimized background therapy only, so there was no evidence of a qualitative interaction with treatment. For the other subgroups, the hypothesis of a similar treatment effect across the levels of the covariate could not be ruled out; these included sex (P=0.23), CCR5 delta32 genotype (P=0.60), viral load at screening (P=0.78), baseline CD4 cell count (P=0.55), the use of enfuvirtide in optimized background therapy (P=0.81), genotypic susceptibility scores (P=0.22), tropism at baseline (P=0.54), the first use of enfuvirtide (P=0.78), and the first use of lopinavir–ritonavir (P=0.93). Since 14 tests for interaction were performed at the 5% significance level, the

probability of at least one test being significant by chance was 0.51 (assuming independence between tests).

Approximately 41% of patients (435 of 1049) received enfuvirtide as part of their optimized background therapy. There was a greater likelihood of complete virologic suppression (i.e., an HIV-1 RNA level of <50 copies per milliliter) in both maraviroc subgroups than in the placebo group, irrespective of the use of enfuvirtide (Fig. 1A). The use of enfuvirtide was categorized as "first use" in 258 of these 435 patients (59%). Regardless of the treatment group, more patients in this subgroup had an HIV-1 RNA level of less than 50 copies per milliliter than did patients with enfuvirtide use that was not categorized as first use (Fig. 2B). Similar results were seen for the first use of the protease inhibitors lopinavir–ritonavir and tipranavir, although the numbers were small (Fig. 2B). Across all of the subgroups in this analysis, patients receiving maraviroc were more likely than patients receiving optimized background therapy only to have a complete virologic response (Fig. 2B).

### IMMUNOLOGIC EFFICACY IN SUBGROUPS

In both MOTIVATE studies, patients who received maraviroc had a significantly greater increase in CD4 cell counts from baseline than did patients who received placebo.[3] The subgroup analysis was consistent with these data, showing a clear trend toward an increased CD4 cell response in patients receiving maraviroc for all subgroups that included baseline CD4 cell counts and viral loads at screening (Fig. 3). There was no evidence that the maraviroc effect seen overall varied according to patient subgroup.

### SAFETY DATA IN PATIENTS WITH HBV AND HCV COINFECTION

The number of patients coinfected with HCV or HBV who were enrolled in the MOTIVATE studies was small. The rates of coinfection with HCV were 4% in the group receiving maraviroc once daily, 7% in the group receiving maraviroc twice daily, and 10% in the placebo group. The rates of coinfection with HBV were 5% in the group receiving maraviroc once daily, 7% in the group receiving maraviroc twice daily, and 8% in the placebo group. For this reason, interactions were not investigated.

Increases in the alanine aminotransferase level of grade 2 or higher from baseline occurred in 1 of 20 patients with HBV coinfection in the group receiving maraviroc once daily, 3 of 27 patients in the group receiving maraviroc twice daily, and 0 of 17 patients in the placebo group. Maximum on-treatment values of grade 3 or 4 were recorded in 0 of 20 patients in the group receiving maraviroc once daily and in 1 of 27 patients in the group receiving maraviroc twice daily, as compared with 1 of 17 patients in the placebo group. More patients with HCV coinfection receiving maraviroc had baseline abnormalities of grade 2 or higher (3 of 15 patients receiving maraviroc once daily and 5 of 29 patients receiving maraviroc twice daily), as compared with the placebo group (1 of 19 patients). Maximum on-treatment values of grade 3 or 4 were reported in 3 of 15 patients receiving maraviroc once daily, 3 of 29 patients receiving maraviroc twice daily, and 1 of 19 patients receiving placebo. Analysis of aspartate aminotransferase values for both subgroups of patients with coinfection showed similar results.

In patients with coinfection, maraviroc did not appear to influence the incidence of adverse events, as compared with placebo (see the Supplementary Appendix, available with the full text of this article at www.nejm.org).

### CHANGES IN VIRAL TROPISM

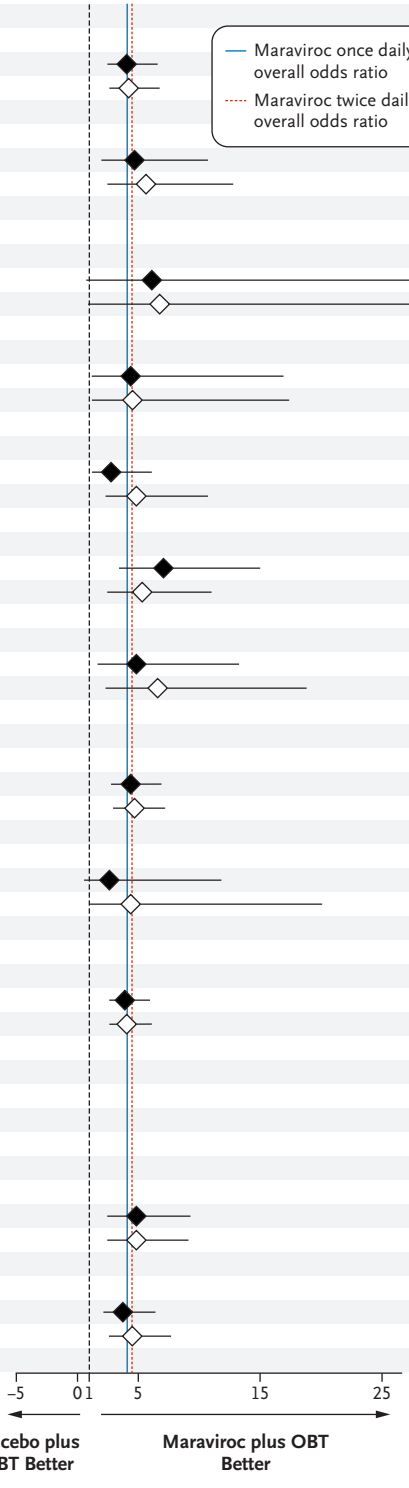
Seven patients who did not have a CCR5 tropism result at screening were incorrectly included: four patients had a dual or mixed tropism result, one patient had a CXCR4-tropism result, and two patients had a result that could not be reported or phenotyped. Of the 1042 patients with an R5 tropism result at screening, 79 patients (8%) had a different tropism result at baseline (all dual or mixed).

In the 83 subjects who had dual or mixed tropism at baseline, the rate of virologic suppression was 18% in the placebo group (3 of 17 patients), as compared with 30% in the group receiving maraviroc once daily (10 of 33 patients) and 27% in the group receiving maraviroc twice daily (9 of 33 patients). The test for an interaction between treatment and tropism at baseline was not significant ($P=0.54$).

Treatment failed and there was a reportable tropism result at failure for 228 patients with an R5 tropism result at baseline. Among these pa-

A

| Subgroup | HIV-1 RNA <50 Copies/ml at Wk 48 *no. of patients/total no. (%)* | P Value for Interaction: Once daily | P Value for Interaction: Twice daily |
|---|---|---|---|
| Screening viral load | | 0.74 | 0.53 |
| <100,000 copies/ml | | | |
| MVC once-daily group | 140/238 (58.8) | | |
| MVC twice-daily group | 142/243 (58.4) | | |
| Placebo | 32/123 (26.0) | | |
| ≥100,000 copies/ml | | | |
| MVC once-daily group | 55/170 (32.3) | | |
| MVC twice-daily group | 61/176 (34.7) | | |
| Placebo | 8/84 (9.5) | | |
| Baseline CD4 count | | 0.48 | 0.97 |
| <50 cells/mm$^3$ | | | |
| MVC once-daily group | 13/84 (15.5) | | |
| MVC twice-daily group | 14/85 (16.5) | | |
| Placebo | 1/38 (2.6) | | |
| 50–100 cells/mm$^3$ | | | |
| MVC once-daily group | 19/51 (37.3) | | |
| MVC twice-daily group | 20/55 (36.4) | | |
| Placebo | 3/25 (12.0) | | |
| 101–200 cells/mm$^3$ | | | |
| MVC once-daily group | 39/95 (41.1) | | |
| MVC twice-daily group | 59/104 (56.7) | | |
| Placebo | 12/55 (21.8) | | |
| 201–350 cells/mm$^3$ | | | |
| MVC once-daily group | 79/115 (68.7) | | |
| MVC twice-daily group | 67/116 (57.8) | | |
| Placebo | 13/62 (21.0) | | |
| >350 cells/mm$^3$ | | | |
| MVC once-daily group | 44/62 (71.0) | | |
| MVC twice-daily group | 43/59 (72.9) | | |
| Placebo | 10/26 (38.5) | | |
| Baseline viral tropism | | 0.31 | 0.61 |
| R5 | | | |
| MVC once-daily group | 181/364 (49.7) | | |
| MVC twice-daily group | 187/377 (49.6) | | |
| Placebo | 37/187 (19.8) | | |
| Dual or mixed | | | |
| MVC once-daily group | 10/33 (30.3) | | |
| MVC twice-daily group | 9/33 (27.3) | | |
| Placebo | 3/17 (17.6) | | |
| Clade status | | Too few subjects with non–clade B virus to assess | |
| Clade B | | | |
| MVC once-daily group | 187/385 (48.6) | | |
| MVC twice-daily group | 190/400 (47.5) | | |
| Placebo | 40/197 (20.3) | | |
| Non–clade B | | | |
| MVC once-daily group | 8/19 (42.1) | | |
| MVC twice-daily group | 11/15 (73.3) | | |
| Placebo | 0/7 (0.0) | | |
| ENF in OBT | | 0.63 | 0.93 |
| Yes | | | |
| MVC once-daily group | 77/166 (46.4) | | |
| MVC twice-daily group | 89/180 (49.4) | | |
| Placebo | 17/89 (19.1) | | |
| No | | | |
| MVC once-daily group | 118/242 (48.8) | | |
| MVC twice-daily group | 114/239 (47.7) | | |
| Placebo | 23/118 (19.5) | | |



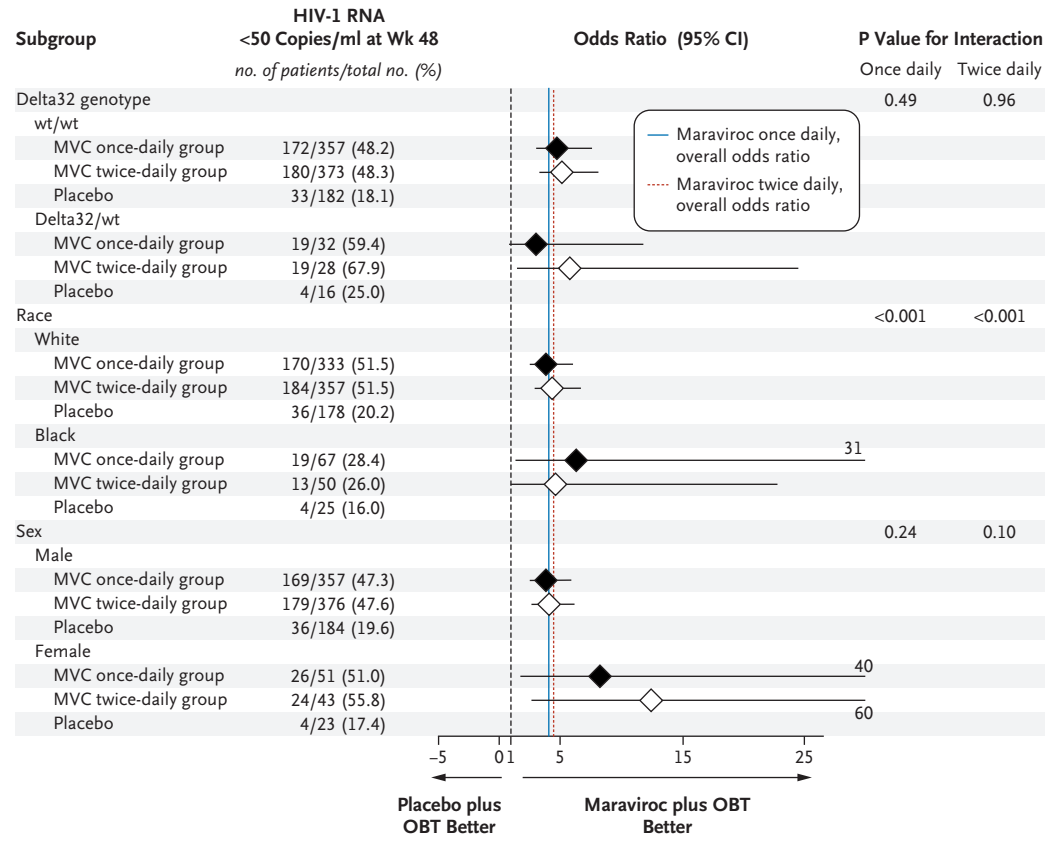



**Figure 1 (facing page). Virologic Efficacy at 48 Weeks in the Subgroup Analysis Population.**

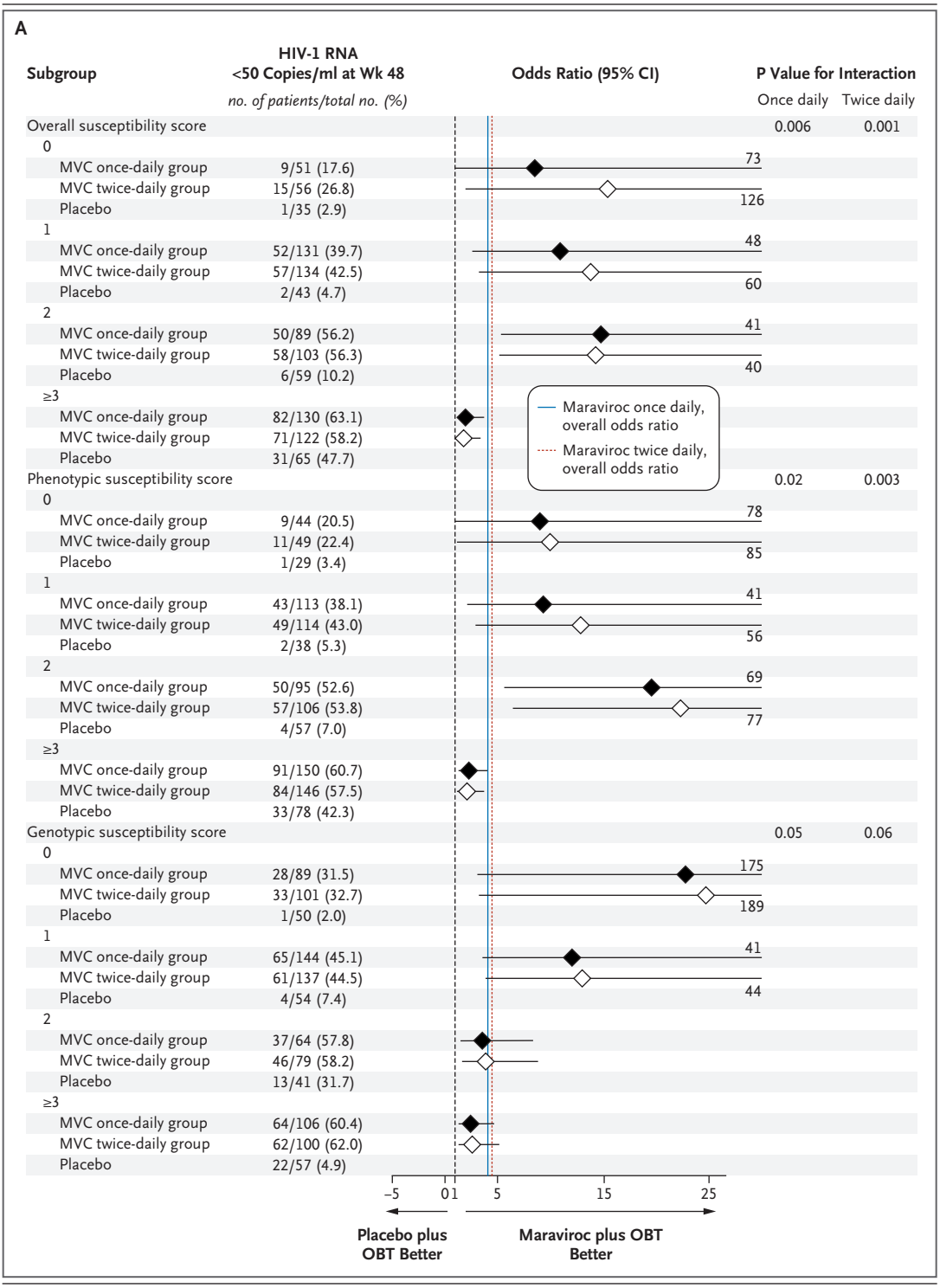
Odds ratios for an HIV-1 RNA level of less than 50 copies per milliliter at week 48 are shown. Panel A shows odd ratios according to the screening viral load, baseline CD4 count and viral tropism, clade status, and use or nonuse of enfuvirtide (ENF) in optimized background therapy (OBT). Panel B shows odd ratios according to the CCR5 delta32 genotype, race, and sex. MVC denotes maraviroc, and wt wild type.

tients, 76 of 133 patients who received maraviroc had a dual or mixed or X4 tropism result (57%) and 57 patients had an R5 tropism result (43%). By comparison, just 6 of 95 patients who received placebo (6%) had virus binding to CXCR4 that was detectable at treatment failure.

There was a higher mean change in the CD4 cell count in patients in whom maraviroc failed than in patients who received placebo (Table 3). Patients with a virus binding to CXCR4 in whom maraviroc failed had a smaller increase in the CD4 cell count from baseline, as compared with patients who had a CCR5 tropism result at the time of failure; however, even in this population, the increase in the CD4 cell count from baseline was still higher than that in the overall placebo group. Evaluation of the time to failure indicated that among patients with a virus binding to CXCR4 in whom treatment failed, the failure occurred approximately 2 months earlier than among patients with a R5 tropism result in whom treatment failed. The median time to failure of once-daily maraviroc was 113 days among patients with the virus binding to CXCR4 versus 176 days among patients with a R5 tropism result. The median time to failure of twice-daily maraviroc was 98 days among patients with the virus binding to CXCR4 versus 149 days among patients with a R5 tropism result.

## DISCUSSION

The primary analyses of the data from week 48 in the MOTIVATE studies showed the virologic and immunologic benefit of maraviroc in the treatment



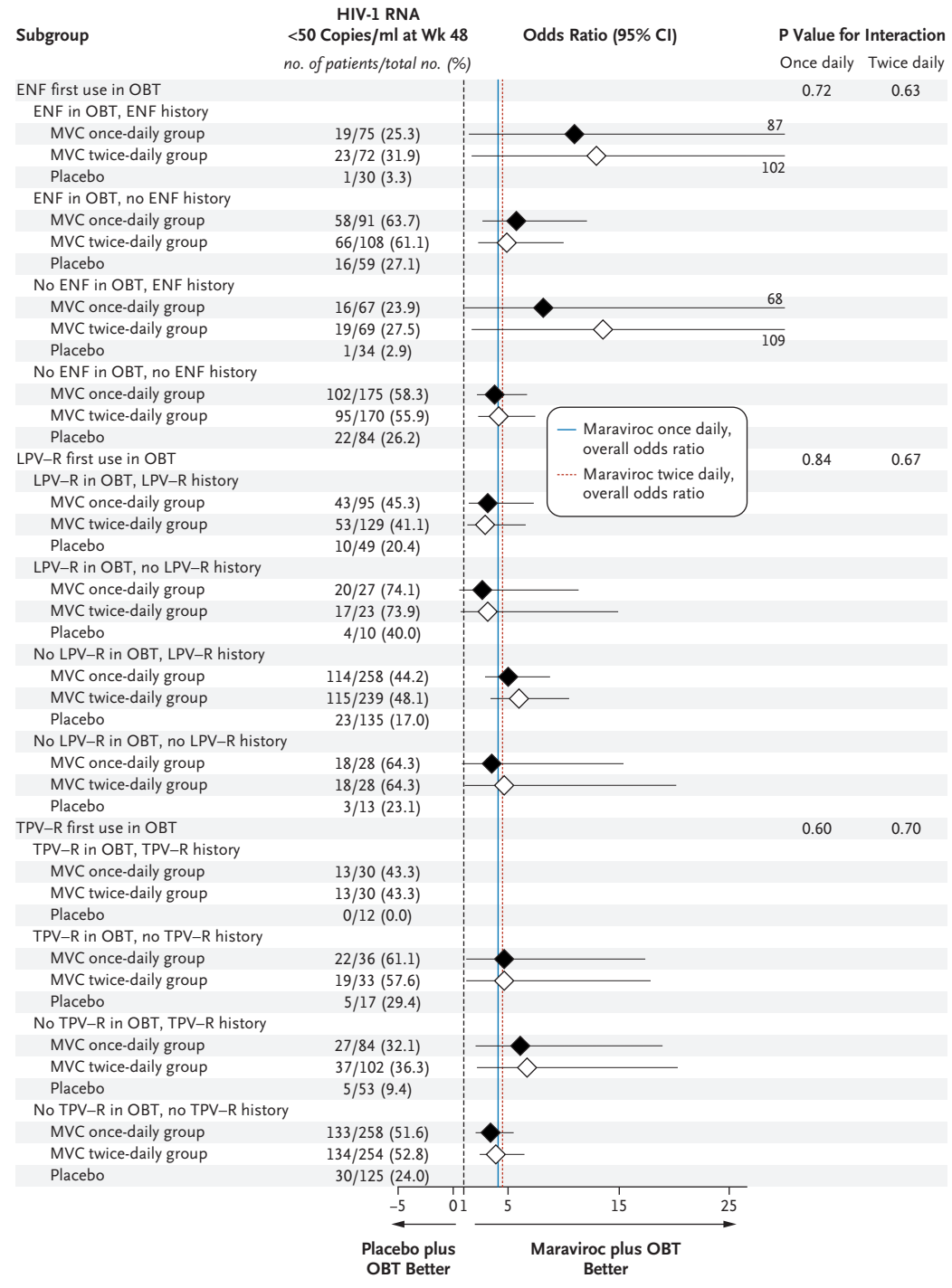



**Figure 2 (facing page). Virologic Efficacy at 48 Weeks in the Subgroup-Analysis Population.**

Odds ratios for an HIV-1 RNA level of less than 50 copies per milliliter at week 48 are shown. Panel A shows odds ratios according to susceptibility scores at screening. Panel B shows odds ratios according to the use or nonuse of enfuvirtide (ENF), lopinavir–ritonavir (LPV–R), and tipranavir–ritonavir (TPV–R) in optimized background therapy (OBT). MVC denotes maraviroc.

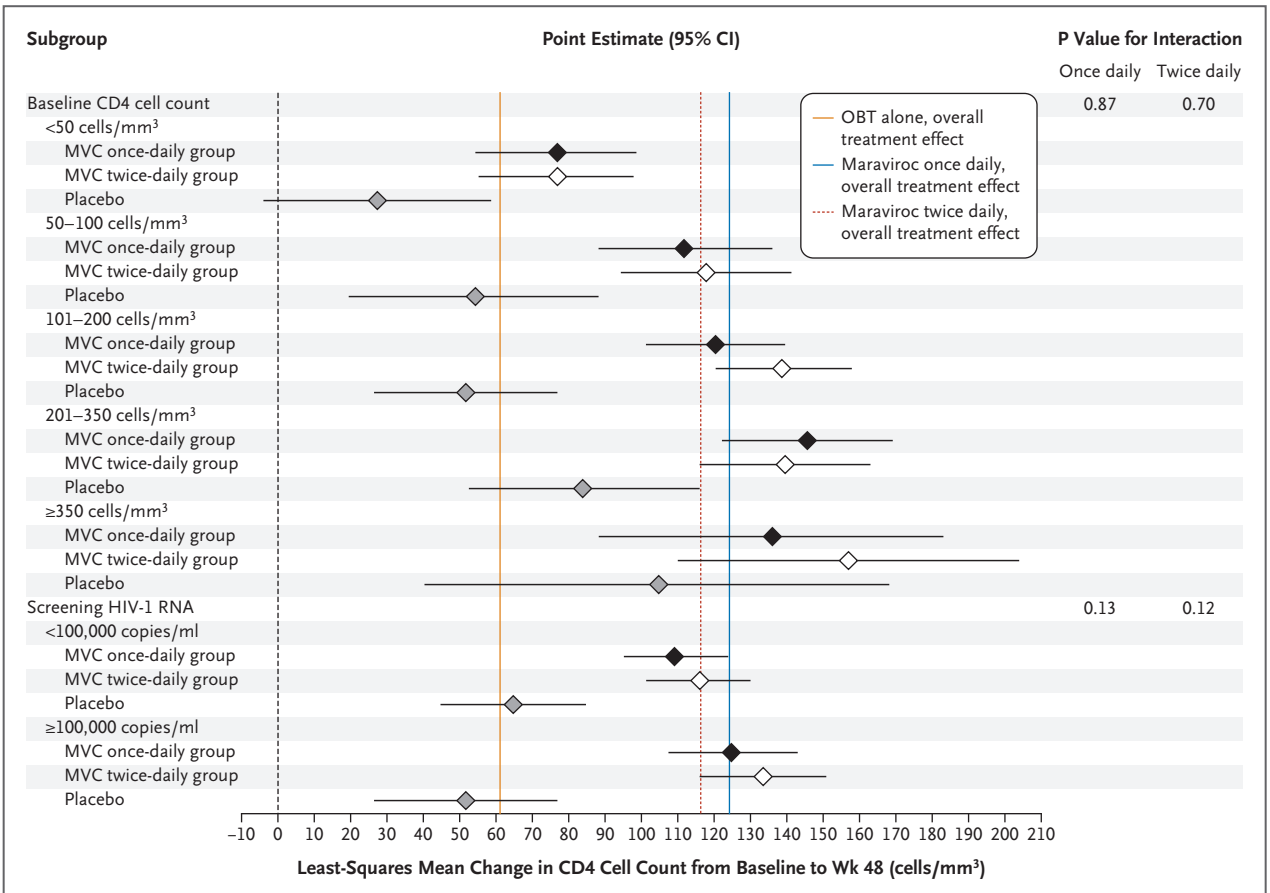



**Figure 3. Least-Squares Mean Change in the CD4 Cell Count at Week 48 According to the Baseline CD4 Cell Count and the Screening HIV-1 RNA Level.**

of patients with clinically advanced R5 HIV-1 infection.[3] Subgroup analyses according to key baseline variables confirmed a consistent treatment benefit for patients who received maraviroc, including subgroups of patients with a low baseline CD4 cell count or high viral load at the time of screening — these are generally considered to be negative prognostic factors.[23,24] In addition, treatment with maraviroc provided sustained virologic efficacy as compared with placebo, even in patients with no potentially active drugs in their optimized background therapy according to calculated susceptibility scores.

The effects of maraviroc given once daily or twice daily were very similar across all subgroups — findings that are consistent with the data from the overall population. However, twice-daily dosing is recommended on the basis of data at week 24 that showed that more patients treated with maraviroc twice daily who had a CD4 cell count below 50 cells per cubic millimeter, an HIV-1 RNA level above 100,000 copies per milliliter, or an overall susceptibility score of 0 at screening had an undetectable viral load at 24 weeks, with no evidence of an increased safety risk.[25] This recommendation was also supported by a population pharmacokinetic analysis showing that more patients in the twice-daily group had a target concentration ($C_{avg}$) of 100 ng per milliliter or greater, which was associated with an increased likelihood of a virologic response.[26,27]

The analysis of response according to the first use of key background drugs shows the additional beneficial effect of including a potent, fully active new drug in the background regimen when therapy with maraviroc is initiated. These findings are consistent with data from studies of other antiretroviral agents with activity against HIV-1 that are resistant to established agents,[4,28-30] and they provide support for the current treatment guide-

**Table 3. CD4 Cell Count at Treatment Failure According to Tropism.***

| CD4 Cell Count | Placebo plus Optimized Background Therapy (N=209) | Maraviroc Once Daily plus Optimized Background Therapy (N=414) | Maraviroc Twice Daily plus Optimized Background Therapy (N=426) |
|---|---|---|---|
| All patients with treatment failure† | | | |
| No. of patients | 111 | 92 | 96 |
| Increase from baseline — cells/mm³ (95% CI) | 24 (10 to 40) | 64 (47 to 82) | 74 (56 to 92) |
| Patients with R5 HIV-1 at baseline and R5 at treatment failure† | | | |
| No. of patients | 89 | 33 | 24 |
| Increase from baseline — cells/mm³ (95% CI) | 25 (8 to 42) | 77 (40 to 115) | 133 (88 to 178) |
| Patients with R5 HIV-1 at baseline and dual or mixed or X4 at treatment failure† | | | |
| No. of patients | 6 | 35 | 41 |
| Increase from baseline — cells/mm³ (95% CI) | 61 (–15 to 138) | 47 (27 to 66) | 57 (32 to 82) |
| Patients with non–R5 HIV-1 at baseline and any tropism at treatment failure‡ | | | |
| No. of patients | 10 | 16 | 21 |
| Increase from baseline — cells/mm³ (95% CI) | 34 (–21 to 89 ) | 67 (25 to 109) | 29 (3 to 54) |

* R5 HIV-1 virus denotes HIV-1 virus with a CCR5 tropism.
† The mean change in the CD4 cell count from baseline in patients with treatment failure is shown. A last-observation-carried-forward approach was used to impute missing values. Data on patients with a missing tropism result that could not be reported or phenotyped at treatment failure were not included in this table. A total of 24 patients had isolates that could not be amplified or a tropism result that could not be reported or phenotyped at treatment failure.
‡ The results include patients with a tropism result that could not be reported or phenotyped at baseline.

lines that recommend the use of at least two, and preferably three, fully active agents in a new regimen in patients with evidence of virologic resistance.[31]

Despite the concerns regarding the hepatic safety of CCR5 antagonists,[12] an analysis of the data from week 48 in the MOTIVATE studies did not show a significant difference in severe hepatotoxic effects between maraviroc and placebo.[3] Furthermore, earlier concern that CCR5 antagonists may have a negative effect in patients with HCV coinfection[15] were not supported by a detailed review and a meta-analysis of the published literature on CCR5 genotype expression and HCV.[16] Although the MOTIVATE studies were not specifically designed to address this issue and the overall number of patients with coinfection was small, no evidence of increased hepatotoxic effects in patients who received maraviroc was found in this subgroup. An absence of increases in hepatotoxic effects or HCV viremia has also been reported in a study of another CCR5 antagonist, vicriviroc, in patients with HCV coinfection.[32] Thus, concerns regarding a potential negative class effect of CCR5 antagonists in patients with viral hepatitis are not substantiated by the currently available results of clinical studies.

The proportion of patients in the placebo group in whom therapy failed was more than double that observed in the maraviroc treatment groups. However, with regard to the tropism result at the time of failure, more than 50% of patients who received maraviroc had virus binding to CXCR4, as compared with only 6% who received placebo. This finding is consistent with the increased sensitivity for detection of low levels of preexisting virus binding to CXCR4 when CCR5-tropic variants are selectively suppressed, and it is analogous to the outgrowth of preexisting (archived) drug-resistant virus leading to reduced efficacy when failed antiretrovial therapy is reinitiated after the interruption of treatment.[33] Given the concern that emergence of the virus binding to CXCR4 could be associated with a decline in the CD4 cell count and clinical progression,[34] it is reassuring that this was not observed. Even in patients with virus binding to

CXCR4 in whom maraviroc failed, there was still a greater increase in the CD4 cell count at the time of failure than there was for patients in the placebo group. The more pronounced increases in the CD4 cell count in patients with a CCR5-tropic virus in whom maraviroc failed could be explained by a longer duration of treatment. Overall, our observations suggest that the clinical consequences of the evolution of the X4 virus during treatment with a CCR5 antagonist may be different from the consequences of the emergence of the X4 virus in the natural course of infection.

The changes in tropism results from screening to baseline observed in 8% of patients are consistent with the limits of sensitivity of the currently used assay,[21] and they are similar to data from another study.[9] These changes are probably related to shifting viral subpopulations, with a minority subpopulation of virus binding to CXCR4 not detected at screening but subsequently detected at a level at or above the limit of sensitivity of the assay.[10] There was no evidence of a detrimental effect on the virologic or immunologic outcome in these patients. Although the numbers included in this analysis are small, these results are consistent with the data from another study involving patients with a dual or mixed HIV-1 tropism.[35] Therefore, the assay can safely be used in clinical practice to screen patients for CCR5 tropism and the likelihood of a virologic response to a CCR5 antagonist.

There is a need for effective, conveniently administered antiretroviral agents with an acceptable adverse event and side-effect profile for patients with adverse prognostic factors, multidrug-resistant HIV-1 infection, or both who have received treatment previously. The results of these subanalyses of pooled data from week 48 in the MOTIVATE studies are encouraging in this respect, and they suggest that maraviroc provides a valuable additional treatment option for a wide spectrum of patients with R5 virus infection who have been previously treated.

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