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Influence of Sex/Gender and Race on Responses to Raltegravir Combined With Tenofovir-Emtricitabine in Treatment-Naive Human Immunodeficiency Virus-1 Infected Patients: Pooled Analyses of the STARTMRK and QDMRK Studies.

Kathleen E. Squires
Thomas Jefferson University

Linda-Gail Bekker
The Desmond Tutu HIV Centre

Christine Katlama
Hopital Pitié Salpetriere

Yazdan Yazdanpanah
Hopital Bichat-Claude Bernard

Yan Zhou
Merck and Co., Inc.

See next page for additional authors

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MAJOR ARTICLE

Influence of Sex/Gender and Race on Responses to Raltegravir Combined With Tenofovir-Emtricitabine in Treatment-Naive Human Immunodeficiency Virus-1 Infected Patients: Pooled Analyses of the STARTMRK and QDMRK Studies

Kathleen Squires,[1] Linda-Gail Bekker,[2] Christine Katlama,[3] Yazdan Yazdanpanah,[4] Yan Zhou,[5] Anthony J. Rodgers,[5] Mark J. DiNubile,[5] Peter A. Sklar,[5] Randi Y. Leavitt,[5] and Hedy Teppler[5]

[1]Department of Medicine, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania; [2]Department of Medicine, The Desmond Tutu HIV Centre, University of Cape Town, South Africa; [3]Department of Infectious Diseases, Hopital Pitié Salpetriere, and [4]Department of Infectious and Tropical Diseases, Hopital Bichat-Claude Bernard, Paris, France; [5]Merck & Co., Inc., Kenilworth, New Jersey

Background. Antiretroviral therapy in human immunodeficiency virus (HIV)-infected women and blacks merits particular scrutiny because these groups have been underrepresented in clinical trials.

Methods. To document the effects of raltegravir across sex and racial lines, we conducted a pooled subgroup analysis of the efficacy and safety of raltegravir 400 mg BID plus tenofovir-emtricitabine by sex (women vs men) and self-identified race (black vs non-black) using phase 3 studies in treatment-naive patients.

Results. Study participants included 42 black women, 102 non-black women, 48 black men, and 477 non-black men. Clade B infections were less common in women (43.8%) than men (84.6%) and in blacks (45.6%) than non-blacks (80.5%). Baseline CD4 counts were ≤200 cells/μL in 52.2% of blacks and 31.6% of non-blacks. Black men had the largest proportion of patients with baseline CD4 counts <50 cells/μL and the highest nontreatment-related discontinuation rate among the 4 sex-by-race subgroups. Human immunodeficiency virus-ribonucleic acid levels <50 copies/mL were achieved at week 48 in 92.7% (95% confidence interval [CI], 80.1–98.5) of black women, 93.6% (95% CI, 86.6–97.6) of non-black women, 82.9% (95% CI, 67.9–92.8) of black men, and 91.4% (95% CI, 88.4–93.8) of non-black men. Serious clinical adverse events were reported in 9.0% of women versus 8.8% of men and in 11.1% of blacks versus 8.5% of non-blacks.

Conclusions. In this post hoc analysis of patients with previously untreated HIV-1 infection receiving raltegravir plus tenofovir-emtricitabine, generally comparable results were achieved across sex and racial subgroups. However, black men had a lower response rate than either black women or non-black men, partially attributable to lower baseline CD4 counts and higher discontinuation rates.

Keywords. QDMRK; raltegravir; STARTMRK; subgroup analyses.

Human immunodeficiency virus (HIV) infection continues to present major public health challenges in both developing and developed nations. According to the World Health Organization [1], there were over 1 million deaths from HIV-related causes and approximately 2 million new infections in 2014. The enduring burden of HIV in women, including mother-to-child transmission, was late to be recognized and remains inadequately addressed. Currently for women in their reproductive years, HIV is the leading cause of death worldwide [1]. The response to HIV infection was especially slow to be addressed in women and minority populations. This blunted early response to the global HIV epidemic continues to exact an immense toll on women and blacks, particularly in sub-Saharan Africa where most new HIV infections are occurring. Disparities in care persist in resource-constrained regions of the world as well as in industrialized countries such as the United States [2, 3]. Underserved populations consisting disproportionately of poor blacks and women now constitute the large majority of people living with HIV around the globe [1–3].

Although drug side-effects may be different and sometimes more prominent in women than men, the efficacy of antiretroviral regimens has been thought to be reasonably comparable in both sexes [3–9]. For example, women report more nausea and less diarrhea than men [9]. On the other hand, lower response rates have been reported in black patients relative to whites or Asians [9–11]. For example, at week 48 in treatment-naive,

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Correspondence: K. Squires, Division of Infectious Diseases, Jefferson University Hospital, 1015 Chestnut Street, Suite 1020, Philadelphia, PA 19107 (kathleen.squires@jefferson.edu).

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HIV-1-infected patients enrolled in the phase 3 ECHO and THRIVE trials, sex differences in efficacy were not apparent, whereas response rates were lower among black compared with non-black patients irrespective of treatment [9].

Emerging data from the recently completed noninferiority Women Antiretroviral Efficacy and Safety (WAVES) study suggest that not all regimens in common use among women are equivalent. This as-yet unpublished landmark trial exclusively enrolled 575 treatment-naive women from 80 sites around the world, comparing a single-pill combination of tenofovir, emtricitabine, and elvitegravir boosted with cobicistat to tenofovir-emtricitabine plus ritonavir-boosted atazanavir [12]. Noninferiority was first established, and then superiority of the elvitegravir arm was sequentially inferred. The difference in response rates between regimens was not fully explained by differential medication adherence in the study arms.

Raltegravir, as part of combination antiretroviral therapy, has proven efficacious and well tolerated in most HIV-1 infected patients without obvious differences among sex or racial subgroups [13–16]. In individual randomized trials, responses in women and blacks treated with raltegravir appeared to be similar to the results observed in other demographic groups [13–17]. Likewise, comparable efficacy across sex and racial lines was observed in REALMRK, an international, open-label, single-arm study of raltegravir-based therapy specifically designed to generate data for HIV-positive patients traditionally underrepresented in pivotal clinical trials [18].

In the phase 3 STARTMRK study of treatment-naive patients, the overall efficacy of raltegravir was at least noninferior to the results with efavirenz when used in combination with tenofovir-emtricitabine through 5 years of therapy, including at the primary endpoint of 48 weeks [15, 16]. QDMRK was a later noninferiority trial of treatment-naive patients comparing the standard raltegravir dosage of 400 mg BID to an 800 mg QD schedule, each given with tenofovir-emtricitabine [17]. Noninferiority of once-daily dosing with the standard formulation of raltegravir was not demonstrated relative to the approved twice-daily regimen at the primary 48-week endpoint. The safety and efficacy results from these large trials did not appear to vary by sex or race. However, the numbers of participants from understudied populations in each randomized controlled study were small relative to the proportions of white men enrolled [19].

To better document responses to raltegravir along sex and racial lines, we conducted a pooled subgroup analysis of the efficacy and safety of raltegravir 400 mg BID combined with tenofovir-emtricitabine by sex (women vs men) and self-identified race (black vs non-black) using composite data from the 2 aforementioned randomized, double-blind, international studies of treatment-naive HIV-infected patients [15, 17]. Results through the initial 48 weeks of treatment were chosen for this post hoc analysis because these data were available from both studies and week 48 was the primary endpoint in each trial.

METHODS

Parent Study Designs

STARTMRK (MK-0518 Protocol 021; clinicaltrials.gov identifier NCT00369941) and QDMRK (MK-0518 Protocol 071; clinicaltrials.gov identifier NCT00745823) were international, blinded, randomized, active-controlled phase 3 clinical trials [15, 17]. The studies were approved by the institutional review boards at each participating institution and conducted in accordance with Good Clinical Practice guidelines. All participants provided written informed consent. The primary analyses for both studies were performed at week 48 as specified by protocol.

Previously untreated HIV-1-infected patients ≥18 years of age were eligible if their viral ribonucleic acid (vRNA) levels were >5000 copies/mL, and the isolated virus was susceptible to all study drugs at entry. Patients were stratified by screening vRNA levels and viral hepatitis coinfection status. After stratification, patients were randomly assigned in a 1:1 ratio to receive a standard raltegravir or comparator regimen (efavirenz in STARTMRK and raltegravir 800 mg QD in QDMRK), each in combination with coformulated tenofovir-emtricitabine.

Human immunodeficiency virus RNA levels were measured by the COBAS Amplicor HIV-1 Monitor assay (version 1.5; Roche Diagnostics, Branchburg, NJ) with a lower limit of quantification of 400 vRNA copies/mL and the Ultrasensitive Amplicor HIV-1 Monitor assay (version 1.5; Roche Diagnostics) with a lower quantification limit of 50 vRNA copies/mL.

Statistical Analyses

For STARTMRK and QDMRK, all patients treated with raltegravir 400 mg BID combined with tenofovir-emtricitabine were included in the primary analyses at week 48. For calculation of virologic response rates, the protocols stipulated that the primary approach to handling missing data would be to include all noncompleters as failures (NC = F). The results using the NC = F approach to missing data only counted patients with vRNA levels <50 copies/mL at the specified time point as successes. An observed-failure (OF) approach allowing evaluation of drug efficacy without confounding by discontinuations due to intolerability or nontreatment-related reasons was also prespecified as a secondary efficacy analysis as well as for assessing changes in baseline CD4 cell counts and for the planned subgroup efficacy analyses based on demographic and prognostic factors at baseline.

In the current pooled subgroup analysis, patients who had self-identified as multiracial were included as non-blacks. The proportion of patients with vRNA levels <50 copies/mL and the mean change from baseline CD4 cell counts at week 48 were summarized by sex and race with 95% exact confidence intervals (CIs). For between-subgroup differences, 95% CIs were calculated by the method of Miettinen and Nurminen [20] with weights proportional to the size of each stratum. Both the NC = F and OF approaches were used for missing vRNA results in parallel analyses. With the OF approach,

patients who discontinued for lack of efficacy were counted as failures thereafter and their baseline CD4 cell counts were carried forward to week 48, whereas patients discontinuing prematurely for other reasons were not included at subsequent time points. Recognizing the potential of confounding by covariates (such as region of origin and infecting clade), interaction effects between sex and race on response rates were tested by a logistic model as an exploratory analysis.

All reported adverse events occurring while on treatment or in the 14 days after discontinuation of therapy during the initial 48 weeks of each study were included in the present analysis. Clinical and laboratory adverse events and worsening grades for prespecified laboratory parameters were tallied. Adverse events were considered to be drug related when judged by the site investigator as definitely, probably, or possibly related to any of the study drugs. The intensity of clinical adverse events was rated by the investigator as mild, moderate, or severe. The severity of laboratory abnormalities was graded according to the 1992 DAIDS toxicity guidelines for adults.

RESULTS

Baseline Characteristics and Patient Accounting

Of the 669 patients who received raltegravir 400 mg BID in STARTMRK and QDMRK, 144 (21.5%) were women (mean age, 38.5 years) and 525 (78.5%) were men (mean age, 38.0 years), and 90 (13.5%) were black (mean age, 38.5 years) and 579 (87%) were non-black (mean age, 38.1 years) (Table 1).

Table 1. Baseline Characteristics of Patients Treated With Raltegravir 400 mg BID in the STARTMRK and QDMRK Trials by Sex and Race[a]

Characteristic	Black Women (N = 42)	Non-black Women (N = 102)	Black Men (N = 48)	Non-black Men (N = 477)
Study, n (%)				
STARTMRK	12	42	21	206
QDMRK	30	60	27	271
Region, n (%)				
Latin America	2 (4.8)	34 (33.3)	6 (12.5)	126 (26.4)
Southeast Asia	0 (0.0)	28 (27.5)	0 (0.0)	31 (6.5)
South Africa	16 (38.1)	1 (1.0)	4 (8.3)	2 (0.4)
United States/Canada	12 (28.6)	7 (6.9)	26 (54.2)	129 (27.0)
EU/Australia	12 (28.6)	32 (31.4)	12 (25.0)	189 (39.6)
Age, in years				
Mean (SD)	40.1 (10.7)	37.8 (11.6)	37.0 (9.3)	38.1 (9.4)
Median (range)	39.0 (23–71)	35.0 (19–67)	36.0 (20- 63)	38.0 (20–69)
CD4 Cell Count, Cells/μL				
Mean (SD)	191.4 (112.7)	240.3 (121.3)	212.4 (146.7)	266.1 (132.9)
Median (range)	189.5 (4–507)	237.5 (2–577)	197.0 (1–555)	260.5 (1–803)
History of AIDS, n (%)				
Yes	1 (2.4)	13 (12.7)	5 (10.4)	33 (6.9)
Viral Subtype, n (%)				
Clade B	10 (23.8)	53 (52.0)	31 (64.6)	413 (86.6)
Non-Clade B	32 (76.2)	49 (48.0)	17 (35.4)	60 (12.6)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.8)
Viral Hepatitis Status, n (%)				
Positive HBV or HCV	2 (4.8)	6 (5.9)	5 (10.4)	30 (6.3)
Baseline Plasma HIV RNA, n (%)				
≤50 000 copies/mL	13 (31.0)	45 (44.1)	20 (41.7)	154 (32.3)
>50 000 copies/mL	29 (69.0)	57 (55.9)	28 (58.3)	323 (67.7)
≤100 000 copies/mL	25 (59.5)	62 (60.8)	26 (54.2)	250 (52.4)
>100 000 copies/mL	17 (40.5)	40 (39.2)	22 (45.8)	227 (47.6)
≤500 000 copies/mL	38 (90.5)	95 (93.1)	43 (89.6)	433 (90.8)
>500 000 copies/mL	4 (9.5)	7 (6.9)	5 (10.4)	44 (9.2)
Baseline CD4 Cell Counts, n (%)				
≤50 cells/μL	6 (14.3)	10 (9.8)	11 (22.9)	27 (5.7)
>50 to ≤200 cells/μL	17 (40.5)	23 (22.5)	13 (27.1)	123 (25.8)
>200 cells/μL	19 (45.2)	69 (67.6)	24 (50.0)	326 (68.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

Abbreviations: AIDS, acquired immune deficiency syndrome; EU, European Union; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; N, number of patients in each group; n (%), number (percentage) of patients in each category; RNA, ribonucleic acid; SD, standard deviation.

[a] Patients who self-identified as multiracial were included as non-blacks.

Table 2. Patient Disposition at Week 48

Disposition	Black Women (N = 42)	Non-black Women (N = 102)	Black Men (N = 48)	Non-black Men (N = 477)
Completed 48 wks	40 (95.2)	92 (90.2)	41 (85.4)	448 (93.9)
Discontinued by week 48	2 (4.8)	10 (9.8)	7 (14.6)	29 (6.1)
Lack of Efficacy	0 (0.0)	1 (1.0)	0 (0.0)	8 (1.7)
Clinical adverse event	0 (0.0)	3 (2.9)	1 (2.1)	6 (1.3)
Consent withdrawn	0 (0.0)	2 (2.0)	0 (0.0)	2 (0.4)
Lost to follow up	0 (0.0)	0 (0.0)	3 (6.3)	7 (1.5)
Protocol deviation	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.2)
Physician decision	0 (0.0)	0 (0.0)	1 (2.1)	3 (0.6)
Pregnancy	1 (2.4)	2 (2.0)	0 (0.0)	0 (0.0)
Other	1 (2.4)	1 (1.0)	2 (4.2)	2 (0.4)

Patients treated in the 2 trials had generally similar baseline characteristics overall, except that patients in STARTMRK had lower median CD4 counts (212 vs 278 cells/μL) than in QDMRK.

Overall, the female cohort had a lower proportion of white patients (36.8% vs 63.8%) and higher proportions of black (29.2% vs 9.1%) and Asian (20.1% vs 7.6%) patients than the male cohort. Infection with clade B virus was less common among women (43.8%) than among men (84.6%). Baseline vRNA levels were >100 000 copies/mL in 39.6% of women and 47.4% of men (overall means, 4.8 [standard deviation; SD = 0.6] and 4.9 [SD = 0.6] $\log_{10}$ copies/mL, respectively). Baseline CD4 cell counts were ≤200 cells/μL in 38.9% of women and 33.1% of men (overall means, 226.0 [SD = 120.6] vs 261.1 [SD = 135.0] cells/μL, respectively).

Overall, the black cohort had a higher proportion of women (46.7%) than the non-black cohort (17.6%). Although the majority of black men were enrolled in North America (26 of 48 [54.2%] vs 4 of 48 [8.3%] from Africa), the largest number of black women were South African (16 of 42 [38.1%] vs 12 of 42 [28.6%] African Americans). Infection with clade B virus was less common among black patients (45.6%) than among non-black patients (80.5%), likely a consequence of the disproportionate enrollment of the black patients (particularly black women) from sub-Saharan Africa. Baseline vRNA levels were >100 000 copies/mL in 43.3% of blacks and 46.1% of non-blacks (overall means, 4.9 [SD = 0.6] $\log_{10}$ copies/mL for both the black and non-black subgroups). Baseline CD4 cell counts were ≤200 cells/μL in 52.2% of blacks and 31.6% of non-blacks; mean and median CD4 counts at baseline were lower in the black cohort (202.6 and 193.0 cells/μL, respectively) than in the non-black cohort (261.5 and 255.0 cells/μL, respectively). The largest proportion of patients with baseline CD4 counts <50 cells/μL among the 4 sex-by-race subgroups were black men (22.9%), followed by black women (14.3%).

A total of 91.7% of women and 93.1% of men completed 48 weeks of treatment in both studies (Table 2). Other than pregnancy, the reasons for discontinuation were comparable among women and men except that 10 men (1.9%) and no women were lost to follow up. A total of 90.0% of black patients and 93.3% of non-black patients completed 48 weeks of treatment. Black patients were more likely to discontinue for reasons unrelated to treatment than non-black patients; no black patient discontinued due to lack of efficacy. Among the 4 subgroups, discontinuation rates were highest for black men (14.6%)—more than double the rates in either non-black men (6.1%) or black women (4.8%).

Virologic and Immunologic Responses

Using an OF approach to missing data, generally consistent virologic and immunologic effects were observed across sex or racial groups through the initial 48 weeks of therapy (Figure 1). At week 48, vRNA levels <50 copies/mL were achieved in 93.3% of women (126 of 135) and 90.7% of men (458 of 505) (difference: +2.6%; 95% CI, −3.3 to +7.0). The mean change in CD4 cell count from baseline to week 48 was + 189.1 cells/μL in women and + 194.4 cells/μL in men (difference: −5.3 cells/μL; 95% CI, −31.1 to +20.5). At week 48, vRNA levels <50 copies/mL were achieved in 87.8% of blacks (126 of 135) and 91.8% of non-blacks (458 of 505) (difference: −4.0%; 95% CI, −13.0 to +2.1). The mean change in CD4 cell count from baseline to week 48 was + 182.4 cells/μL in blacks and + 194.9 cells/μL in non-blacks (difference: −12.6 cells/μL; 95% CI, −43.9 to +18.8).

Using an OF approach to missing data, vRNA levels <50 copies/mL were achieved at week 48 in 38 of 41 (92.7%; 95% CI, 80.1–98.5) black women, 88 of 94 (93.6%; 95% CI, 86.6–97.6) non-black women, 34 of 41 (82.9%; 95% CI, 67.9–92.8) black men, and 424 of 464 (91.4%; 95% CI, 88.4–93.8) non-black men; the respective increments in CD4 counts from baseline were 147.8 (95% CI, 120.5–175.0), 207.4 (95% CI, 181.5–233.2), 217.0 (95% CI, 168.0–265.9), and 192.4 (95% CI, 179.7–205.0) cells/μL. Of the 4 sex-by-race subgroups, black men were the least likely to have vRNA levels <50 copies/mL; this observation was more pronounced with the NC = F than OF method of handling missing data, likely due to black men having a higher discontinuation rate unrelated to treatment than the other subgroups (Tables 3 and 4). A later analysis separating the 59 patients identifying themselves as multiracial from those considered as non-black revealed that this subgroup had numerically higher response rates for both women and men than other "non-blacks" or "blacks" using either the NC = F (93.2%; 95% CI, 83.5–98.1) or OF (94.8%; 95% CI, 85.6–98.9) approaches to missing data. Black men experienced the numerically greatest increment in CD4 cell counts, whereas black women had the smallest increase.

Safety and Tolerability

The types of adverse events in each of the 4 sex-by-race subgroups are shown in Table 5. The causes of the 2 deaths were reported as Kaposi's sarcoma at week 8 in a 27-year-old black man and cerebral hemorrhage at week 13 in 57-year-old Asian man.

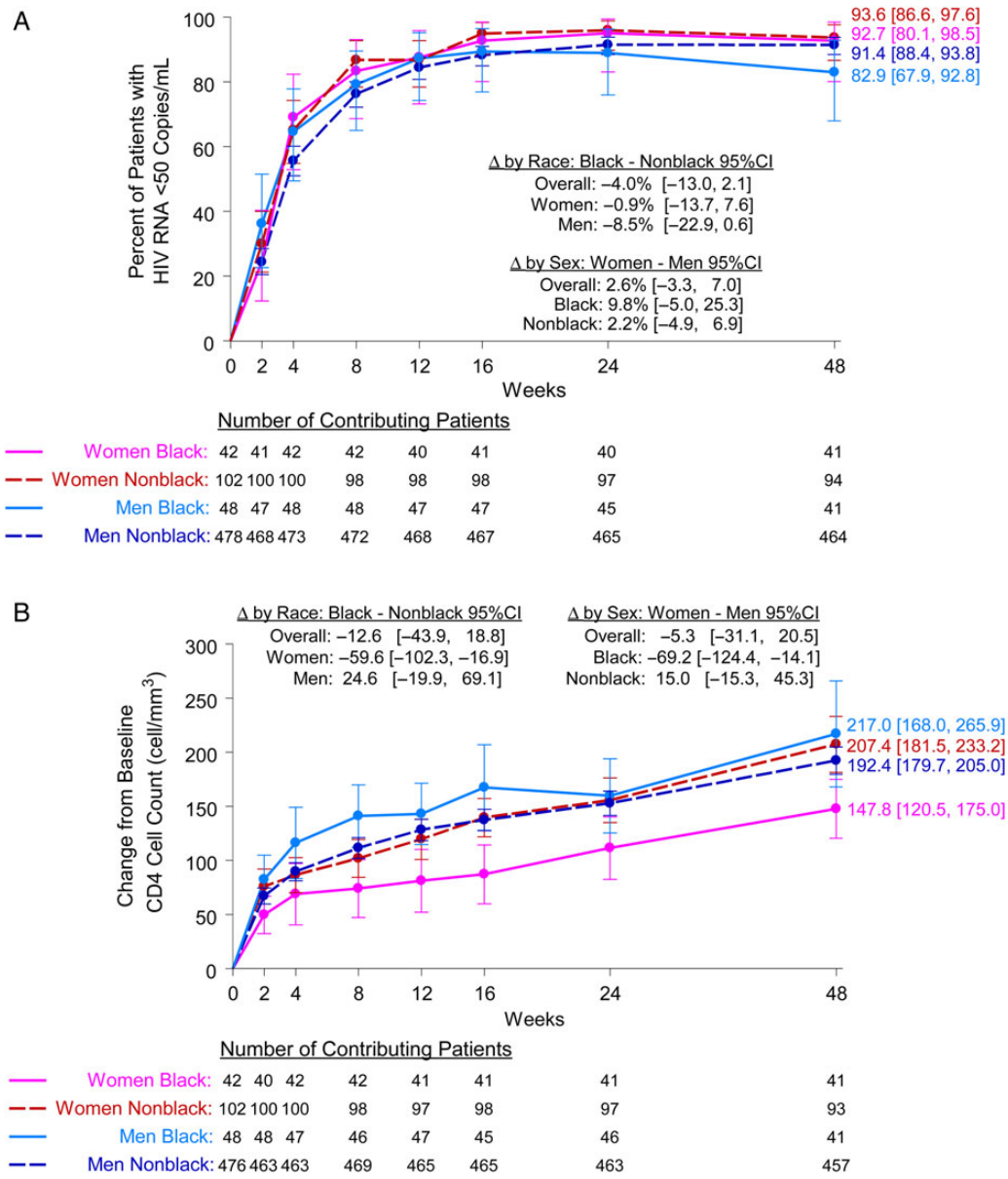

Figure 1. Time course of virologic response rate (confirmed viral ribonucleic acid level <50 copies/mL) (A) and CD4 cell count increment from baseline (B). Graphs are displayed for the 4 sex-by-race subgroups through the initial 48 weeks of the pooled studies. Missing data were handled using an observed-failure approach. Abbreviation: CI, confidence interval.

During the initial 48 weeks of the studies, clinical adverse events were reported in 123 (85.4%) of the 144 women and 466 (88.8%) of the 525 men and led to treatment discontinuation in 3 (2.1%) women and 8 (1.5%) men. Drug-related clinical adverse events were reported in 50 (34.7%) women and 166 (31.6%) men. Serious clinical adverse events were

Table 3. Percentage of Patients With vRNA Level <50 copies/mL at Week 48 by Sex by Race Using the Noncompleter as Failure Approach to Missing Data

	Total (Women + Men)	Women	Men	Sex Difference (Women – Men) [95% CI]
Total (black + non-black)	87.3 [84.5 to 89.7]	87.5 [81.0 to 92.4]	87.2 [84.1 to 90.0]	0.3 [–6.6 to 5.8]
Black	80.0 [70.2 to 87.7]	90.5 [77.4 to 97.3]	70.8 [55.9 to 83.0]	19.6 [3.2 to 35.5]
Non-black	88.4 [85.5 to 90.9]	86.3 [78.0 to 92.3]	88.9 [85.7 to 91.6]	–2.6 [–11.0 to 3.7]
Race difference (black – non-black) [95% CI]	–8.4 [–18.2 to –0.9]	4.2 [–9.5 to 14.4]	–18.1 [–32.3 to –6.7]	Test for sex-by-race interaction $P = .016$

Abbreviation: CI, confidence interval; vRNA, viral ribonucleic acid.

Table 4. Percentage of Patients With vRNA Level <50 copies/mL at Week 48 by Sex by Race Using the Observed-Failure Approach to Missing Data

	Total (Women + Men)	Women	Men	Sex Difference (Women – Men) [95% CI]
Total (black + non-black)	91.3 [88.8 to 93.3]	93.3 [87.7 to 96.9]	90.7 [87.8 to 93.1]	2.6 [–3.3 to 7.0]
Black	87.8 [78.7 to 94.0]	92.7 [80.1 to 98.5]	82.9 [67.9 to 92.8]	9.8 [–5.0 to 25.3]
Non-black	91.8 [89.2 to 93.9]	93.6 [86.6 to 97.6]	91.4 [88.4 to 93.8]	2.2 [–4.9 to 6.9]
Race difference (black – non-black) [95% CI]	–4.0% [–13.0 to 2.1]	–0.9% [–13.7 to 7.6]	–8.5% [–22.9 to 0.6]	Test for sex-by-race interaction $P = .456$

Abbreviation: CI, confidence interval; vRNA, viral ribonucleic acid.

reported in 13 women (9.0%) and 46 men (8.8%). Laboratory adverse events occurred in 12 (8.3%) women and 51 (9.7%) men and were considered to be drug related in 4 (2.8%) women and 17 (3.2%) men. No serious laboratory adverse events were reported in either group.

Clinical adverse events were reported in 79 (87.8%) of the 90 black patients and 510 (88.1%) of 579 non-black patients, with treatment discontinuations precipitated by a clinical adverse event occurring in 1 (1.1%) and 10 (1.7%) patients, respectively. Drug-related clinical adverse events were reported in 27 (30.0%) blacks and 189 (32.6%) non-blacks. Serious clinical adverse events were reported in 10 black patients (11.1%) and 49 non-black patients (8.5%), including 7 (14.6%) of 48 black men. Laboratory adverse events occurred in 8 (8.9%) black patients and 55 (9.5%) non-black patients and were considered to be drug related in 1 (1.1%) black patient and 20 (3.5%) non-black patients. No serious laboratory adverse events were reported in either group. Decreased absolute neutrophil counts on therapy were more common among black than non-black patients (grade 2–4, 17% vs 2%, respectively); other laboratory changes were generally similar across racial subgroups.

DISCUSSION

The efficacy and safety of antiretroviral therapy in HIV-infected women and blacks require special attention because these groups have historically been underrepresented in pivotal clinical trials and underserved around the world [1–3, 19]. The combined demographics for patients randomized to the raltegravir 400 mg BID arms in STARTMRK and QDMRK indicate that only 22% were woman and 13% self-identified as black [15, 17]. Biological and psychosocial factors based on sex or race could influence therapeutic responses [7, 10, 11, 21–28].

Generally consistent virologic and immunologic effects with an overall similar safety profile were maintained across sex and racial subgroups treated with raltegravir plus tenofovir-emtricitabine. However, some numerical variations were observed in subpopulations. In the current analysis of treatment-naive patients, discontinuation rates were higher for black men than for either non-black men or black women, but these differences were not attributable to more adverse events or lower efficacy. The lowest response rates were likewise seen in black men, a trend also recognized in treatment of hepatitis C infection [29].

Table 5. Types and Frequencies of Reported Clinical and Laboratory Adverse Events During the Initial 48 Weeks of the Studies[a]

	Clinical Adverse Events				Laboratory Adverse Events			
	Black Women	Non-black Women	Black Men	Non-black Men	Black Women	Non-black Women	Black Men	Non-black Men
Number of patients	42	102	48	477	42	102	48	477
with 1 or more AE	39 (92.9)	84 (82.4)	40 (83.3)	426 (89.3)	3 (7.1)	9 (8.8)	5 (10.4)	46 (9.6)
with drug-related AE[b]	15 (35.7)	35 (34.3)	12 (25.0)	154 (32.3)	0 (0.0)	4 (3.9)	1 (2.1)	16 (3.4)
with serious AE[c]	3 (7.1)	10 (9.8)	7 (14.6)	39 (8.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
with serious drug-related AE[b]	0 (0.0)	2 (2.0)	0 (0.0)	4 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
who discontinued due to AE[d]	0 (0.0)	3 (2.9)	1 (2.1)	7 (1.5)[§]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
who discontinued due to drug-related AE[b]	0 (0.0)	1 (1.0)	0 (0.0)	4 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
who discontinued due to serious AE	0 (0.0)	3 (2.9)	1 (2.1)	4 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
who discontinued due to serious drug-related AE[b]	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
who died[c]	0 (0.0)	0 (0.0)	1 (2.1)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: AE, adverse event; N, number of patients in each group; n, number (percentage) of patients in each category; n/N, frequency (%) of the stipulated AE.

[a] All treated patients were included in the safety analysis. All AEs occurring during the first 48 weeks of the study were tallied. The frequencies of adverse events were not adjusted for the duration of follow up.

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

[c] Neither of the 2 deaths were judged to be drug related.

[d] The discontinuations in the table refer to discontinuation of study medications (even if the patient remained in the study). One non-black man had stopped treatment but remained in the study at week 48.

This finding was more prominent with the NC = F than OF method of handling missing data, consistent with the relatively high drop-out rate observed among black men due to nontreatment-related issues and thus suggesting nonvirologic reasons for the differences. On the other hand, black men, who were the most likely group to have baseline CD4 cell counts <50 cells/μL, experienced the numerically greatest increment in CD4 cell counts, whereas black women had the smallest increase.

REALMRK was a multicenter, open-label, single-arm study designed with the purpose of enrolling a diverse cohort of HIV-infected patients from the United States, Brazil, Dominican Republic, Jamaica, and South Africa [18]. In contrast to our population, most patients were treatment-experienced. Of the 206 participants, 97 (47%) were women and 153 (74%) were black. All received standard raltegravir-based regimens. Overall, 15% of patients discontinued, including 13% of men, 18% of women, 14% of blacks, and 17% of non-blacks. At study week 48, response rates were similar for men versus women and black versus non-black patients. In contrast, there were differences observed in drug-related clinical adverse events reported by men (8%) versus women (18%) and blacks (14%) versus non-blacks (9%).

The limitations of our retrospective study should be explicitly acknowledged. Although a pooled analysis was justified based on similarities in trial design and baseline patient characteristics in the 2 parent studies, extrapolation of these findings must be done cautiously because subgroup analyses are inherently subject to potential bias caused by imbalances in known and unrecognized covariates. Subgroups created by dividing study participants by both sex and race had small numbers (other than for white men); accordingly, further breakdown of the sub-subgroups by baseline prognostic factors was not performed. Patients self-identified their sex or gender and race; patients who self-identified as multiracial were included as non-blacks in all cases. The rationale underlying the somewhat arbitrary categorization was that the racial components of "multi-racial" were not collected on the case-report forms. Self-identification as black was thus used to assign race in our analysis because this determination likely mimicked the real-world perception most faithfully. Ethnicity was not differentiated separately in STARTMRK. Possible confounders when comparing sex and racial subgroups include (1) baseline vRNA levels and CD4 counts, (2) use of prophylactic interventions for opportunistic interventions, (3) mode of HIV acquisition and ongoing risk behaviors, and (4) regional variation in healthcare systems and the distribution of HIV subtypes. We did not collect data on specific HIV risk factors or the likely mode of HIV transmission. Medication adherence in black men may have been compromised by the relatively high frequency of serious adverse events despite their continuing in the study, although we could not reliably confirm or exclude this possibility.

Clinical trial results may not always predict real-world effectiveness. The complex issues impacting the course of HIV infection in subpopulations extend far beyond the specific choice of antiretroviral drugs [7, 11, 12, 21–28, 30]. The interaction of sex and race on the efficacy and safety of treatment is complicated by both modifiable and immutable covariates such as the interplay of risk behaviors, genetic and biological predispositions, psychosocial factors, medication access and adherence, comorbidities, ethnicity and culture, country of residence, education, and socioeconomic status.

CONCLUSIONS

In our retrospective analysis, the efficacy and safety of raltegravir plus tenofovir-emtricitabine appeared to be generally comparable across sex or racial subgroups with previously untreated HIV-1 infection. However, response rates were lower among black men than in other subpopulations, which could be partly explained by the higher discontinuation rates unrelated to treatment in this subgroup. Strategies to mitigate treatment discontinuation and suboptimal follow-up among black men in clinical trials and in real-world practice are deserving of explicit attention [31, 32].

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Principal Investigators

STARTMRK

The MK-0518 Protocol 021 principal investigators are listed alphabetically by country: Australia: Cooper D.; Brazil: Madruga J., Netto E., Zajdenverg R.; Canada: Baril J. G., Kovacs C., Smaill F.; Chile: Afani A., Beltran C., Perez Godoy J.; Colombia: Angela M., Arango A., Tamara J., Velez J.; France: Cotte L., Girard P.-M., Pialoux G., Salmon-Ceron D., Yazdanpanah, Y; Germany: Esser S., Fatkenheuer G., Rockstroh J. K., Schmidt R., Stellbrink H.-J.; India: Dinaker M., Pazare A., Rajendran J., Srivastava O; Italy: Carosi G., Chirianni A., Esposito R., Lazzarin A., Viscoli C.; Mexico: Andrade J., Quintero Perez N., Reyes G., Sierra J., Torres I.; Peru: Gotuzzo E., Lama

J., Cabello-Chavez R., Salazar R.; Spain: Portilla Sogorb J., Rivero-Roman A., Santamaria Jauregui J.; Thailand: Manosuthi W., Sungkanuparph S., Supparatpinyo K., Vibhagool A.; United States: Berger D., DeJesus E., Friel T., Hicks C., Kozal M., Kumar P., Lennox J., Liporace R., Little S., Morales-Ramirez J., Novak R., Pollard R., Saag M., Santiago S., Schneider S., Steigbigel R., Towner W., Wright D.

QDMRK

The MK-0518 Protocol 071 principal investigators are listed alphabetically by country: Australia: Bloch M. T., Hoy J., Workman C.; Brazil: Madruga J. V., Souza T., Telles F. Q., Zajdenverg R.; Canada: Angel J., Montaner J. S., Smith G. H. R., Trottier B.; Colombia: Tamara J. R., Velez J. D.; Denmark: Gerstoft J., Laursen A. L., Mathiesen L.; France: Katlama C., Molina J. M., Raffi F., Reynes J., Yazdanpanah Y.; Germany: Bogner J. R., Fatkenheuer G., Hartl H., Jaeger H., Kuhlmann B., Lutz T., Van Lunzen J.; Greece: Daikos G. K., Giamarellou H. J., Gargalianos-Kakolyris P., Lazanas M., Skoutelis A. T.; India: Dinaker M., Shobha V., Srivastava O.; Italy: Antinori A., Cauda R., Mezzaroma I., Narciso P.; Mexico: Andrade J., Crabtree B.; Netherlands: Brinkman K., Geerlings S. E., Van Der Ende M. E.; Peru: Cabello R. L.; Portugal: Antunes F., Branco T., Marques R.; Puerto Rico: Morales-Ramirez J. O.; Russia: Pokrovsky V. V., Rakhmanova A. G.; South Africa: Botes M. E., Grimwood A., Ive P., Johnson D. W., Mohapi L.; Spain: Aguirrebengoa-Ibarguren K., Arribas Lopez J. R., Berenguer-Berenguer J., Gatell Artigas J. M.; Switzerland: Battegay M., Cavassini M., Hirschel B. J., Weber R.; Thailand: Anekthananon T., Sungkanuparph S., Supparatpinyo K.; United Kingdom: Fisher M., Nelson M. R., Youle M.; United States: Bellos N. C., Brown S. J., Campo R. E., Cook P. P., Corales R., DeJesus E., Fish D. G., Friel T. J., Gathe J., Hargan R.T., Kinder C., Kumar P., Larsen R. A., Markowitz M., Marquez F., McDonald C. K., Mills A., Mullane K. M., Nahass R., Osiyemi O. O., Rashbaum B. S., Redfield R. R., Rhame F., Rixinger A. I., Ruane P. J., Santiago S., Scarsella A. J., Shalit P.; Squires K. E., Stanse J., Tedaldi E. M., Torres J. G., Towner W. J., Waldman L. F., Young B.

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