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MAJOR ARTICLE

Phase 2 Study of the Safety and Tolerability of Maraviroc-Containing Regimens to Prevent HIV Infection in Men Who Have Sex With Men (HPTN 069/ACTG A5305)

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Background. Maraviroc (MVC) is a candidate for human immunodeficiency virus (HIV) pre-exposure prophylaxis.

Methods. Phase 2 48-week safety/tolerability study was conducted, comparing 4 regimens: MVC alone, MVC plus emtricitabine (FTC), MVC plus tenofovir disoproxil fumarate (TDF), and TDF plus FTC. Eligible participants were HIV-uninfected men and transgender women reporting condomless anal intercourse with ≥1 HIV-infected or unknown-serostatus man within 90 days. At each visit, assessments, laboratory testing, and counseling were done. Analyses were intention to treat.

Results. Among 406 participants, 84% completed follow-up, 7% stopped early, and 9% were lost to follow-up; 9% discontinued their regimen early. The number discontinuing and the time to discontinuation did not differ among study regimens ($P = .60$). Rates of grade 3–4 adverse events did not differ among regimens ($P = .37$). In a randomly selected subset, 77% demonstrated detectable drug concentrations at week 48. Five participants acquired HIV infection (4 MVC alone, 1 MVC + TDF; overall annualized incidence, 1.4% [95% confidence interval, .5%–3.3%], without differences by regimen; $P = .32$); 2 had undetectable drug concentrations at every visit, 2 had low concentrations at the seroconversion visit, and 1 had variable concentrations.

Conclusions. MVC-containing regimens were safe and well tolerated compared with TDF + FTC; this study was not powered for efficacy. Among those acquiring HIV infection, drug concentrations were absent, low, or variable. MVC-containing regimens may warrant further study for pre-exposure prophylaxis.

Clinical Trials Registration. NCT01505114.

Keywords. HIV; PrEP; men who have sex with men (MSM); maraviroc; phase 2 clinical trial.

New human immunodeficiency virus (HIV) infections continue to occur and disproportionately affect men who have sex with men (MSM) [1]. HIV pre-exposure prophylaxis (PrEP) with coformulated tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) was associated with a 44% reduction in the rate of HIV acquisition in MSM in the iPrEx study [2]. Randomized efficacy studies reported in 2015 demonstrated that TDF + FTC was associated with an 86% reduction in HIV acquisition in MSM when prescribed daily in the PROUD study [3] or when taken on-demand in the intervention preventive de l'exposition aux risque avec et pour les gays (IPERGAY) study [4]. Current guidelines recommend daily oral HIV PrEP for high-risk individuals [5, 6].

Although effective, in prior studies PrEP with TDF + FTC was associated with gastrointestinal adverse effects in up to 18% of study participants [2, 7–9] and decreased renal function in up to 18% [4, 10–12] and with a small, but statistically significant, loss of bone mineral density [8, 13, 14]. In addition, drug resistance developed in some participants with unsuspected acute HIV infection randomized to TDF-based PrEP in the iPrEx [2] and Partners PrEP studies [7, 15] and rarely, in on-study participants in Partners PrEP [15]. Given that TDF + FTC is recommended among initial HIV treatment options [16, 17],

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increased drug resistance linked to the use of TDF + FTC PrEP could compromise HIV treatment. Increased drug resistance also could compromise the efficacy of TDF + FTC as PrEP [18]. For these reasons, alternative PrEP regimens are needed.

Maraviroc (MVC) is a CCR5 antagonist HIV entry inhibitor that was approved for treatment of HIV infection based on the results of randomized clinical trials in HIV-infected, treatment-experienced participants that demonstrated safety, tolerability, and virologic efficacy [19]. MVC is active against R5 (CCR5-tropic) HIV, which is associated with the majority of acute HIV transmissions [20] and has several favorable properties for an HIV PrEP agent; MVC is concentrated 8–26-fold higher in the rectum compared with plasma [21]. It is prescribed infrequently for HIV treatment [16]. Preclinical efficacy of oral MVC for HIV prevention was demonstrated in a humanized mouse model [22], although other preclinical studies did not demonstrate protection [23, 24]. MVC was generally safe in HIV-infected individuals for ≥5 years without associated renal toxicity [25] and was associated with less bone loss than TDF in a comparative study of HIV-infected individuals [26]. Finally, MVC was generally well tolerated in a 12-week pilot study of HIV-uninfected participants with rheumatoid arthritis [27]. Based on these characteristics, we sought to study the safety and tolerability of MVC-containing HIV PrEP regimens.

METHODS

Study Design and Participants

This was a prospective, randomized, double-blinded, multicenter study of 4 antiretroviral regimens in at-risk, HIV-uninfected men and transgender women who have sex with men. It was conducted in the United States, sponsored by the Division of AIDS (DAIDS) of the US National Institutes of Health through the HIV Prevention Trials Network (HPTN), and cosponsored by the AIDS Clinical Trials Group.

Eligible participants were born male, ≥18 years old, and self-reported condomless anal intercourse with ≥1 man known to be HIV-infected or of unknown HIV serostatus within 90 days before study entry. Eligible participants had adequate baseline safety laboratory results, including a calculated creatinine clearance ≥70 mL/min (Cockcroft-Gault), a nonreactive HIV antibody test (tested at the site with the local standard-of-care assay and subsequently confirmed at the HPTN Laboratory Center with the ARCHITECT HIV Ag/Ab Combo [fourth-generation assay], Abbott Laboratories), and a plasma HIV RNA level below detection within 14 days of study entry. Participants were excluded if they used any antiretroviral drug within 90 days (eg, for PrEP or postexposure prophylaxis [PEP]), reported active injection drug use, or had a reactive HIV test or positive hepatitis B surface antigen. The study was reviewed and approved by the institutional review boards at each of the participating sites; all participants provided written informed consent.

Randomization and Masking

Eligible participants were enrolled and randomly assigned with equal probability to receive 1 of 4 antiretroviral regimens: (1) MVC (Selzentry; ViiV Healthcare); (2) MVC plus FTC, (Emtriva; Gilead Sciences); (3) MVC plus TDF (Viread; Gilead Sciences); or (4) TDF plus FTC (control arm). Doses of the study drugs were as follows: MVC, 300 mg; FTC, 200 mg; and TDF, 300 mg; and the study regimen consisted of 3 pills, including matching placebos, taken together orally once daily.

The computerized randomization method was developed, implemented, and monitored by the Statistical Center for HIV/AIDS Research and Prevention (Fred Hutchinson Cancer Research Center, Seattle), and it was stratified by site using block randomization with a block size of 12, such that approximately equal numbers of participants were assigned to each arm within each site. The site pharmacist received the randomized treatment assignment. All other site staff and investigators were blinded to the randomization assignments until completion of follow-up.

Procedures

After enrollment and randomization, participants were seen at weeks 2, 4, and 8 and then every 8 weeks through week 48. Study drugs were discontinued at week 48, and a final visit was conducted at week 49. At each visit, interval history, targeted physical examination, safety laboratory tests, blood plasma stored for drug concentration measurements, adherence assessments, risk-reduction counseling, condom distribution, and HIV testing were conducted and study drugs were dispensed. Fasting lipid levels were measured at baseline and at weeks 24 and 48. Adherence support was provided at each visit through counselor-guided discussions.

Testing for sexually transmitted infections (chlamydia and gonorrhea nucleic acid testing of urine and rectal swab samples and syphilis serology) was done at entry and weeks 16 or 24 and 40 or 48 and when an individual reported consistent symptoms; participants were referred for treatment. Participants were evaluated at each visit for HIV exposure; those who requested PEP for HIV exposure were referred locally. Participants who started PEP were instructed to hold study medications and undergo repeated HIV testing ≥14 days after completing PEP; if HIV negative, they could resume their study regimen.

Quality assurance and specialized testing was performed at the HPTN Laboratory Center in Baltimore, Maryland. This included quality assurance testing for HIV and confirmation of all HIV seroconversion events; HIV RNA testing was performed retrospectively at the visit before HIV seroconversion to determine whether participants had acute HIV infection at that visit. Antiretroviral drug concentration testing was performed on a random subset of plasma samples from study participants (n = 160) collected at weeks 24 and 48. MVC, FTC, and tenofovir (TFV) were quantified via validated

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liquid chromatographic–tandem mass spectrometric methods, with assay limits of quantitation of 0.5 ng/mL for MVC and 0.3 ng/mL for FTC and TFV [28, 29]. Additional testing was performed for participants with confirmed HIV seroconversion; this included HIV RNA level, CD4 cell count, antiretroviral drug concentration testing, drug resistance (PhenoSense GT; Monogram Biosciences), and viral tropism testing (Trofile; Monogram Biosciences).

Drug Interaction Substudy

The first 72 participants (18 per study arm) who consented participated in a substudy to evaluate drug interactions between MVC, TFV, and FTC. These participants were reminded not to take study medications the morning of their week 2 visit. Participants had a blood sample collected before drug dosing (steady-state trough concentration), underwent directly observed study drug dosing, and then had another blood sample drawn approximately 6 hours after the observed dose. MVC concentrations in the MVC + FTC and MVC + TDF arms were compared with those in the MVC-alone arm.

Outcomes

The primary outcome was safety and tolerability of the study regimens. Safety was assessed by the investigators as the occurrence of grade 2 (moderate), 3 (severe), or 4 (life-threatening) adverse events [30]. Tolerability was assessed as the proportion of participants who permanently discontinued study drugs and the time to permanent study drug discontinuation through 48 weeks of follow-up. Secondary outcomes included drug-drug interactions and adherence assessed by detectable plasma drug concentrations. Plasma drug concentrations were reported as detectable above the limit of quantitation (all study drugs in the regimen detected) or not. HIV testing was conducted at each visit and whenever HIV infection was suspected; additional testing was performed at the HPTN Laboratory Center to confirm cases of HIV infection.

Statistical Analysis

The planned enrollment was 400 participants (100 per arm) with an assumed 5% loss-to-follow-up rate. The length of the study was estimated at approximately 2 years, with 9 months for accrual and 12-month follow-up of each participant. This sample size was selected to provide sufficient power to detect differences between arms for the tolerability end point (the time to permanent discontinuation of study drugs), and to provide estimates for the true safety end point (occurrence of grade 3 or 4 or higher adverse events through 48 weeks). With the sample of 100 participants per arm, if the true safety adverse event rate was 20%, the estimate would have 95% confidence intervals (CIs) of 12%–28%. The power to detect differences for the tolerability end point was 72% for TDF + FTC versus each of the 3 individual MVC-containing arms when the true hazard ratio is 2.0 and the incidence rate is 30%.

Primary data analysis was performed for all enrolled participants on an intention-to-treat basis. Person-year analysis was performed to summarize and compare the rates of grade 3 or 4 or higher adverse events between any 2 arms. Kaplan–Meier estimates were calculated to summarize the distribution of permanent treatment discontinuation. Analyses of detectable study drug concentrations were performed on a randomly selected subset of week 24 and 48 plasma samples.

Summary statistics were calculated in proportions, means, or event rates in person-years, depending on the variable being binary, continuous, or count, respectively. The χ^2 test was used to compare permanent study drug discontinuation rates, and the log–rank test was used to compare times to permanent study drug discontinuation between any 2 study arms and among the 4 arms. HIV incidence was calculated using the exact method for Poisson counts. Differences were considered statistically significant at $P \leq .05$. The study was reviewed biannually by an independent study monitoring committee of the HPTN, and it was registered at clinicaltrials.gov (NCT01505114).

RESULTS

A total of 406 participants were enrolled in the study between July 2012 and April 2014 and randomized to 1 of 4 study regimens (Figure 1); all but 2 started study drugs, 1 each randomized to MVC + FTC and MVC + TDF. The study population was 100% male at birth, including 7 (2%) who self-identified as female, transsexual, or transgender, with a median age of 30 years (Table 1). Study participants were 28% black, 22% Latino (of any race), and 62% white; 30% were younger than 26 years. Demographic characteristics were balanced between the study arms. During screening, before enrollment, 31 (8%) of the study participants had a total of 34 sexually transmitted infections diagnosed: chlamydia in 15 (4%), gonorrhea in 5 (1%), and syphilis in14 (3%).

Of 406 participants randomized, 343 (84%) completed study follow-up, 28 (7%) stopped the study early, and 35 (9%) were lost to follow-up (Figure 1). The most common reasons for incomplete follow-up were inability to contact the participant (9%) and participant choice to discontinue (3%). One participant died in an automobile accident. Thirty-six (9%) participants permanently discontinued the study regimen before week 48; of these, 11 also terminated study participation, and 26 completed follow-up not taking study medications. There was no difference among the study regimens in the proportion of participants who permanently discontinued study drugs ($P = .60$; Table 2) or in the time to permanent study drug discontinuation ($P = .60$; Table 2 and Figure 2). The most common reasons for early discontinuation of the regimen early were participant request (5%), clinical reasons determined by the investigator (1%), and reactive HIV antibody test(s) (1%; 4 participants). A fifth participant had a reactive HIV antibody test at week 48 (the last visit while taking study medications).

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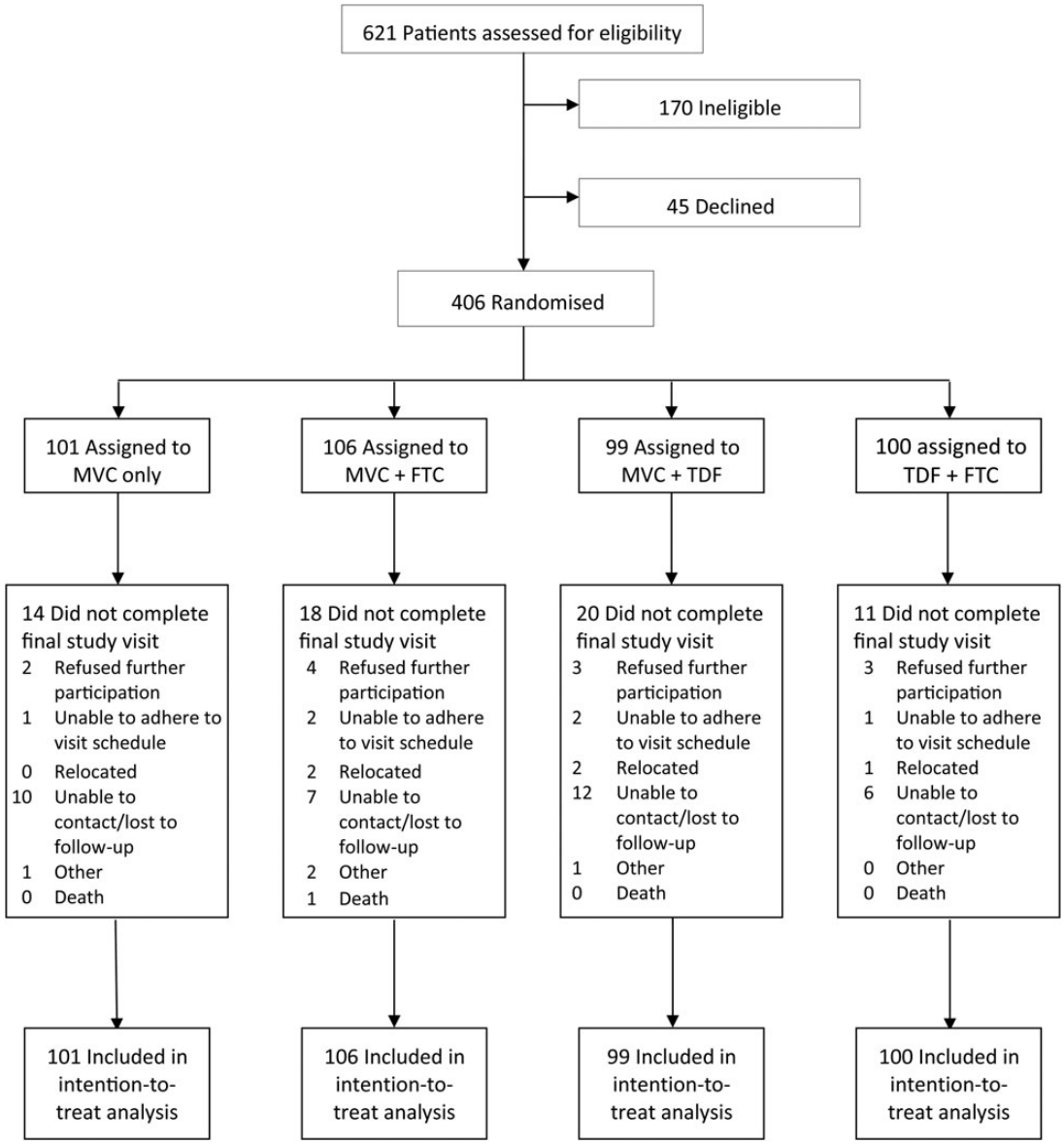

Figure 1. Trial profile. Abbreviations: FTC, emtricitabine; MVC, maraviroc; TDF, tenofovir disoproxil fumarate.

Among the 72 participants in the drug interaction substudy at week 2, the predose (trough) MVC plasma concentrations did not differ significantly among the MVC-alone, MVC + FTC, and MVC + TDF arms in pairwise comparisons after Bonferroni correction (all $P > .05$). There were no significant differences in 6-hour postdose or 6-hour predose MVC concentrations ($P = .64$ and .74, respectively). In a randomly selected subset of 160 participants across the 4 study arms, detectable study drug(s) were documented in 83% of plasma samples at week 24 and 77% at week 48, without significant differences among the arms (week 24, $P = .72$; week 48, $P = .39$). Participants reported at both 24 and 48 weeks that they took a median of 95% of their study medications as recommended, without differences among the study arms.

Fifty-five participants experienced a total of 67 grade 3 or 4 adverse events; there was no difference among the 4 study regimens in the occurrences or rates of these events ($P = .37$; Table 2). Rates of selected gastrointestinal and renal grade 2–4 adverse events were also similar among the study regimens (Table 2). Overall creatinine clearance decreased a median 4% from baseline to week 48, without differences among the study arms ($P = .60$). During study follow-up, 89 participants (22%) had a total of 114 sexually transmitted infections diagnosed: chlamydia in 48 (12%), gonorrhea in 42 (11%), and syphilis in 24 (6%), without differences among the study arms.

Five participants acquired HIV infection during the study: 4 randomized to MVC alone and 1 to MVC + TDF (Table 3).

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Table 1. Baseline Characteristics of the Study Participants

Characteristic	MVC (n = 101)	MVC + FTC (n = 106)	MVC + TDF (n = 99)	TDF + FTC (n = 100)	Total (N = 406)
Sex, born male, %	100	100	100	100	100
Age, median, y	30	29.5	30	31	30
Age range, y	18–65	18–62	18–70	18–60	18–70
Race, %[a]					
American Indian/ Alaskan Native	4	4	1	3	3
Asian	5	1	4	5	4
Black	31	31	30	21	28
Pacific Islander	1	2	1	2	2
White	60	63	59	66	62
Other	11	9	8	11	10
Latino ethnicity, %	21	25	19	23	22
Marital status, %					
Married/partnership	5	4	3	4	4
Living with primary partner	13	11	16	16	14
Not living with primary partner	6	14	14	7	10
Single, divorced, or widowed	76	71	67	72	71
Other	0	0	0	1	0
Employment status, %					
Full-time	47	50	48	65	52
Part-time	21	23	29	18	23
Unemployed	33	26	22	17	25
Educational level, %					
Less than high school	4	5	2	5	3
High school/trade school	22	15	14	13	17
Some college	36	28	42	38	36
Finished college	31	32	25	35	31
Advanced degree	8	20	16	9	13

Abbreviations: FTC, emtricitabine; MVC, maraviroc; TDF, tenofovir disoproxil fumarate.

[a] Participants could self-identify as >1 race.

The overall annualized incidence of HIV was 1.4% (95% CI,.5%–3.3%); HIV incidence in the individual study arms was as follows: MVC alone, 4.5% (95% CI, 1.2%–11.6%); MVC + FTC, 0% (0%–4.0%); MVC + TDF, 1.1% (0.003%–6.0%); and TDF + FTC, 0% (0%–4.0%) ($P = .32$; Figure 3). Four of these 5 participants had the wild-type CCR5 gene, and 1 was heterozygous for the CCR5-Δ32 deletion. At the visit when HIV seroconversion was documented, HIV RNA levels ranged from 981 to 122 150 copies/mL, and CD4 cell counts from 294 to 828 cells/mm^3. All 5 participants had R5 (CCR5-tropic) HIV without genotypic substitutions associated with antiretroviral drug resistance; 1 of 5 of the viral strains demonstrated modestly decreased phenotypic susceptibility to nelfinavir (5-fold) and ritonavir (3-fold) owing to polymorphisms. Of the 5 participants who acquired HIV infection, 2 had undetectable plasma drug levels at every study visit (1 randomized to MVC alone and 1 to MVC + TDF). The 3 others, who were randomized to MVC alone, had MVC levels of 0.7, 6.7, and 145 ng/mL at the seroconversion visit (Figure 4). The expected predose, steady-state geometric mean plasma concentration of MVC dosed at 300 mg/d is 32 ng/mL [31].

DISCUSSION

In this phase 2, prospective, randomized, double-blinded multicenter study, we showed that MVC-containing regimens were generally safe and well tolerated compared with the control regimen of TDF + FTC when assessed for use as HIV PrEP in a population of at-risk men and transgender women who have sex with men. The rates of grade 3/4 and specific adverse events of interest, including gastrointestinal adverse effects, hypophosphatemia, and increased creatinine, were similar among the study arms. It is critical that preventive medications be safe and well tolerated with few attributable adverse effects. TDF is a first-line drug for the treatment of HIV infection, whereas MVC is infrequently used for treatment [16]. With demonstrated comparable safety and tolerability to the standard-of-care regimen in the current study, MVC-containing regimens may warrant further study as an alternative strategy for HIV PrEP.

Adherence is critical for HIV PrEP efficacy [32, 33]. The iPrEx study reported 51% adherence in the subgroup of MSM who did not acquire HIV infection during the study [2]. Notably, IPrEx was blinded, placebo controlled, and conducted at a time when HIV PrEP was an unproven strategy, which could

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Table 2. Adverse Events

Event	MVC (n = 101)	MVC + FTC (n = 106)	MVC + TDF (n = 99)	TDF + FTC (n = 100)	Total (N = 406)	*P* Value
Permanent study drug discontinuations, No. (%) of participants	7 (7)	9 (9)	12 (12)	8 (8)	36 (9)	.60 (χ^2 Test)
Time to permanent study drug discontinuation, median (IQR), d	120 (74–263)	66 (42–222)	113 (42–260)	67 (34–141)	87 (45–210)	.60 (Log–rank test)
Grade 3–4 adverse events, No. of participants; No. of events	13; 15	11; 15	11; 14	20; 23	55; 67	.37 (Likelihood ratio test)
Grade 3 events, No.						
Related to study drug[a,b]	2	2	4	9	17	. . .
Unrelated to study drug[a]	11	10	7	13	41	. . .
Grade 4 events, No.						
Related to study drug[a]	0	0	0	0	0	. . .
Unrelated to study drug[a]	2	3	3	1	9	. . .
Grade 3–4 adverse event rate, per person-year (95% CI)	0.17 (0.09–0.28)	0.16 (0.09–0.27)	0.17 (0.09–0.28)	0.25 (0.16–0.38)	0.19	. . .
Selected adverse events (grade 2–4), %[c]						
Diarrhea	3	8	7	4	5	. . .
Nausea	0	1	4	4	2	. . .
Vomiting	0	0	1	1	0.5	. . .
Unintentional weight loss	0	2	2	1	1	. . .
Hypophosphatemia	18	10	16	22	17	. . .
Increased creatinine	0	1	0	0	0.25	. . .

Abbreviations: CI, confidence interval; MVC, maraviroc; FTC, emtricitabine; IQR, interquartile range; TDF, tenofovir disoproxil fumarate.

[a] The study investigator assessed the relationship of adverse event to study drug.

[b] Grade 3 adverse events related to the study drug included the following: MVC, aspartate aminotransferase [AST] increase and hypophosphatemia; MVC + FTC, hyperlipidemia and hypophosphatemia; MVC + TDF, AST increase, hypophosphatemia [2]; TDF + FTC, alanine aminotransferase increase [2], AST increase, hypersensitivity reaction, hypophosphatemia [4], and neutrophil count decreased.

[c] All events listed are grade 2 with the exception of hypophosphatemia, which included 2 grade 3 events.

have adversely affected adherence. The more recent IPERGAY study reported detectable plasma drug concentrations in 82%–86% of the first 113 men enrolled and went on to demonstrate 86% efficacy in decreasing HIV infection [4]. In addition, of note in the iPrEx [2] and IPERGAY [4] studies, men who had more frequent condomless anal sex tended to be more adherent.

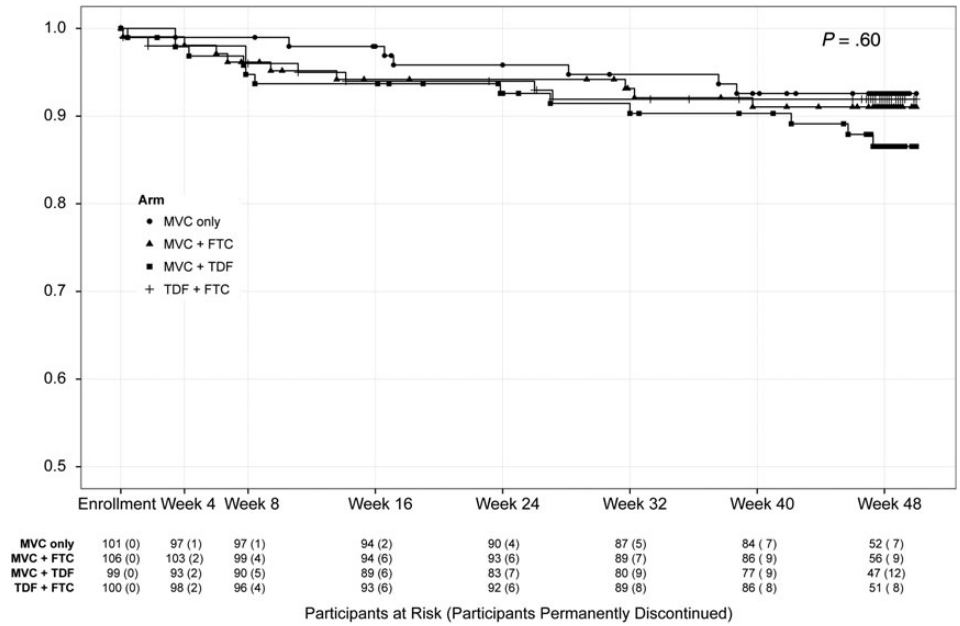

Figure 2. Time to permanent study discontinuation and shown by Kaplan–Meier plot. Abbreviations: FTC, emtricitabine; MVC, maraviroc; TDF, tenofovir disoproxil fumarate.

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Table 3. HIV Infections

Participant	Age, y	HIV Risk Group	Race/ Ethnicity	Study Arm	1st Reactive HIV Test, Study wk	HIV RNA, Copies/ mL	HIV Tropism	Genotypic Drug Resistance	CD4 Cell Count, Cells/ mm^3/%	Study Drug Concentration at Seroconversion Study Visit, ng/mL[a]
1	20	MSM	Black	MVC + TDF	9	122 150	R5	None	357/25	MVC: 0; TFV: 0
2	61	MSM	Asian	MVC	16	981	R5	None[b]	294/20	MVC: 145
3	21	MSM	Mixed race	MVC	28	106 240	R5	None	325/23	MVC: 0
4	35	MSM	White	MVC	38	13 626	R5	None	828/38	MVC: 6.7
5	36	MSM	Black	MVC	48	52 191	R5	None	804/40	MVC: 0.7

Abbreviations: HIV, human immunodeficiency virus; MSM, men who have sex with men; MVC, maraviroc; TDF, tenofovir disoproxil fumarate; TFV, tenofovir.

[a] Concentrations were reported as detectable or not detectable with the following limits of detection: MVC, 0.5 ng/mL; FTC and TFV, 0.3 ng/mL. The expected predose, steady-state geometric mean concentration with MVC dosed at 300 mg/d is 32 ng/mL [31].

[b] Participant 2 was infected with a viral strain that demonstrated 5- and 3-fold reduced phenotypic susceptibility to the HIV protease inhibitors nelfinavir and ritonavir, respectively; all other participants had no reduced phenotypic susceptibility.

In our study conducted at a time when HIV PrEP was known to significantly reduce the risk of HIV infection, our at-risk participants had study drugs detected in >75% of plasma samples tested, suggesting high adherence, although simply detecting antiretroviral drugs is not the same as documenting target drug concentrations.

Prior drug interaction studies conducted in HIV-uninfected volunteers demonstrated the lack of effects of MVC on the pharmacokinetics of nucleoside reverse-transcriptase inhibitors, including zidovudine, lamivudine, and TFV [34]. There were no available data on the interaction of MVC and FTC. We confirmed that there were no significant interactions between MVC and TDF or between MVC and FTC.

Prior preclinical studies explored MVC for prevention of HIV acquisition, and found variable outcomes. Neff et al [22] used a humanized mouse model given MVC orally daily for 7 days with a vaginal HIV challenge on day 4 and reported protection against HIV infection. In contrast, Massud et al [23] used a macaque model given an oral MVC dose 24 hours before rectal exposure and found that 5 of 6 animals acquired simian/human immunodeficiency virus infection by the fifth rectal challenge despite achieving target drug levels. Of note, MVC disassociates 10 times more rapidly from the macaque CCR5 receptor compared with the human CCR5 receptor [35]. Coll et al [24] tested single-dose MVC in human subjects and assessed HIV infectability ex vivo using a rectal tissue explant model, and found a minimal reduction in HIV infection. The investigators attributed this to the loss of approximately 60% of MVC from the biopsy tissue into the culture medium in the first hour and of >90% loss of MVC following overnight incubation. These data suggest that animal and ex vivo models may

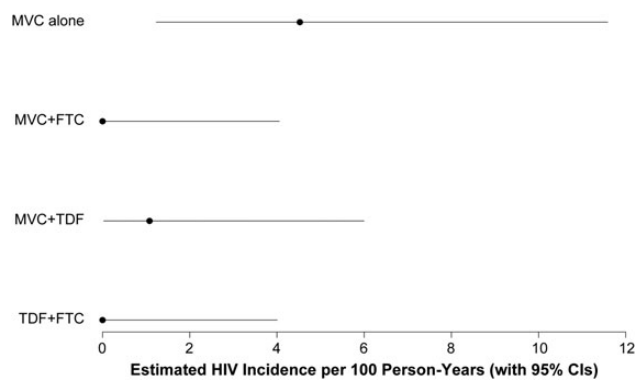

Figure 3. Estimated incidence of human immunodeficiency virus (HIV) infection by study arm, calculated using the exact method for Poisson counts. The overall HIV incidence was 1.4% (95% confidence interval [CI], .5%–3.3%), without differences among the study arms ($P = .32$). Abbreviations: FTC, emtricitabine; MVC, maraviroc; TDF, tenofovir disoproxil fumarate.

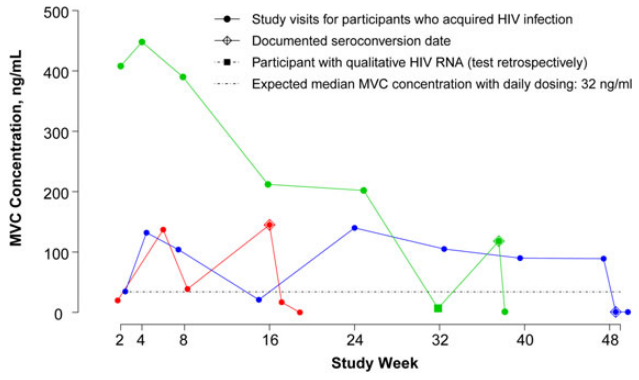

Figure 4. Study drug plasma concentrations over time in participants experiencing human immunodeficiency virus (HIV) seroconversion. Each line presents data from a unique participant who acquired HIV infection and had detectable study drug plasma concentrations; all 3 were randomized to the maraviroc (MVC)–alone arm. Note: 2 other participants who acquired HIV infection, 1 randomized to MVC and 1 to MVC plus tenofovir disoproxil fumarate, had undetectable study drug concentrations at every study visit and are not shown. Diamond points represent study visits at which HIV seroconversion was documented. Boxed points represent visits at which HIV RNA was detected retrospectively; HIV antibody test results at that visit were negative or nonreactive. The expected predose, steady-state geometric mean concentration with MVC dosed at 300 mg/d is 32 ng/mL [31].

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have limitations in predicting the clinical efficacy of MVC-containing regimens for HIV PrEP.

Five study participants acquired HIV infection during our study: 4 randomized to MVC alone and 1 to MVC + TDF. All had R5 (CCR5-tropic) HIV, without evidence of X4 (CXCR4-tropic) virus, and no participant demonstrated drug resistance as assessed with conventional genotypic testing. Notably, 2 of the 5 participants who acquired HIV infection had no detectable study drugs at any visit, and 2 others had MVC plasma concentrations below the expected steady-state concentration at HIV seroconversion. The single participant with an expected MVC concentration documented at the seroconversion visit had concentrations consistent with less than daily dosing for half of his visits, suggesting inconsistent adherence. The similar distribution of new sexually transmitted infections among the study arms suggests that sexual behavior did not differ among the groups. Our phase 2 study was not designed to detect a difference in HIV incidence among the study arms, and no definitive conclusions about comparative efficacy can be made.

There are strengths and limitations of this study. As a prospective, randomized, double-blinded study conducted predominately in at-risk MSM in the United States who were young and racially and ethnically diverse, the results are probably generalizable to one of the populations most in need of HIV PrEP. The active-controlled design ensured that every participant received an antiretroviral drug regimen (ie, there was no all-placebo arm). Frequent follow-up allowed ongoing risk-reduction counseling, adherence support, and testing for HIV and other sexually transmitted infections, which may have promoted adherence. Detection rates of the study medications in plasma were high. Study limitations include the study population who were "at-risk" rather than "high risk" based on self-reported behavior, potentially limiting generalizability. Nearly 80% were highly educated and may have been better informed than prior clinical trial participants about HIV PrEP and perhaps more adherent than prior clinical trials participants. We enrolled few transgender women, limiting our ability to make conclusions for this important at-risk population. The study regimen consisted of 3 pills (2 more than the standard 1-pill TDF + FTC PrEP regimen) and used daily dosing of MVC, although the drug is approved for HIV treatment with twice-daily dosing. Finally, our study was not powered to detect differences in specific adverse events and had limited follow-up.

In summary, we found that MVC-containing HIV PrEP regimens were generally safe and well tolerated compared with the standard-of-care TDF + FTC HIV PrEP regimen. All regimens were associated with high rates of study drug detection in plasma, suggesting our participants were adherent. Although no definitive conclusions about efficacy can be drawn from the current study, the overall annualized HIV incidence rate was low at 1.4%, and did not differ significantly among the 4 study arms ($P = .32$). Although HIV PrEP regimens containing long-acting injectable antiretrovirals or intravenous monoclonal antibodies are under investigation, these regimens may not be ideal for everyone given individual preferences, agent-specific toxic effects, the requirements for repeated and consistent parenteral administration, and the challenges in managing prolonged drug concentrations. Combination MVC-containing oral PrEP regimens may warrant further investigation in fully powered efficacy studies as an alternative to TDF + FTC HIV PrEP.

Notes

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Role of the funding sources. Representatives from DAIDS, Gilead Sciences, and ViiV served on the protocol team. The investigators designed the study; collected, analyzed, and interpreted the data; wrote the manuscript; and made the decision to submit for publication with input from the protocol team. The corresponding author had full access to the data and made the final decision to submit the manuscript.

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