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Maraviroc, as a Switch Option, in HIV-1–infected Individuals With Stable, Well-controlled HIV Replication and R5-tropic Virus on Their First Nucleoside/Nucleotide Reverse Transcriptase Inhibitor Plus Ritonavir-boosted Protease Inhibitor Regimen: Week 48 Results of the Randomized, Multicenter MARCH Study

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Background. Alternative combination antiretroviral therapies in virologically suppressed human immunodeficiency virus (HIV)–infected patients experiencing side effects and/or at ongoing risk of important comorbidities from current therapy are needed. Maraviroc (MVC), a chemokine receptor 5 antagonist, is a potential alternative component of therapy in those with R5-tropic virus.

Methods. The Maraviroc Switch Study is a randomized, multicenter, 96-week, open-label switch study in HIV type 1–infected adults with R5-tropic virus, virologically suppressed on a ritonavir-boosted protease inhibitor (PI/r) plus double nucleoside/nucleotide reverse transcriptase inhibitor (2 N(t)RTI) backbone. Participants were randomized 1:2:2 to current combination antiretroviral therapy (control), or replacing the protease inhibitor (MVC + 2 N(t)RTI arm) or the nucleoside reverse transcriptase inhibitor backbone (MVC + PI/r arm) with twice-daily MVC. The primary endpoint was the difference (switch minus control) in proportion with plasma viral load (VL) <200 copies/mL at 48 weeks. The switch arms were judged noninferior if the lower limit of the 95% confidence interval (CI) for the difference in the primary endpoint was $< -12\%$ in the intention-to-treat (ITT) population.

Results. The ITT population comprised 395 participants (control, n = 82; MVC + 2 N(t)RTI, n = 156; MVC + PI/r, n = 157). Baseline characteristics were well matched. At week 48, noninferior rates of virological suppression were observed in those switching away from a PI/r (93.6% [95% CI, −9.0% to 2.2%] and 91.7% [95% CI, −9.6% to 3.8%] with VL <200 and <50 copies/mL, respectively) compared to the control arm (97.6% and 95.1% with VL <200 and <50 copies/mL, respectively). In contrast, MVC + PI/r did not meet noninferiority bounds and was significantly inferior (84.1% [95% CI, −19.8% to −5.8%] and 77.7% [95% CI, −24.9% to −8.4%] with VL <200 and <50 copies/mL, respectively) to the control arm in the ITT analysis.

Conclusions. These data support MVC as a switch option for ritonavir-boosted PIs when partnered with a 2-N(t)RTI backbone, but not as part of N(t)RTI-sparing regimens comprising MVC with PI/r.

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Keywords. maraviroc; switch; HIV-1; antiretroviral; comorbidity.

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Widespread use of combination antiretroviral therapy (cART) has transformed human immunodeficiency virus type 1 (HIV-1) infection into a chronic condition, with near-normal life expectancy [1]. Recommended regimens are currently 3-drug combinations including at least 2 of the 4 classes of ART (https://aidsinfo.nih.gov/guidelines). While treatment-limiting toxicities have been reduced considerably in recent years, even low-grade side effects

can affect adherence and patient satisfaction [2]. Several switch studies have explored novel antiretroviral combinations. Early findings from some very small nucleos(t)ide reverse transcriptase inhibitor (N(t)RTI)–sparing switch studies [3–5] including maraviroc (MVC) [6, 7] have been encouraging, but none are definitive.

MVC, the first licensed [8] chemokine receptor 5 (CCR5)-receptor antagonist, targets a host co-receptor critical for HIV entry into $CD4^+$ T-cells and monocyte/macrophages. MVC is safe and well tolerated, with favorable renal and lipid profiles (http://www.selzentry.com). These factors are likely to be of increasing importance as the HIV-infected population ages with greater risks of increased cardiovascular disease (CVD) and declining renal function. MVC may also have additional anti-inflammatory activity that could further reduce risks of specific end-organ disease [9].

A key barrier to using MVC in routine care settings is the need for characterization of virus co-receptor tropism prior to use. Assay systems can now determine HIV co-receptor tropism based not only on HIV RNA but also on HIV DNA [10, 11]. The latter means tropism for the CCR5 co-receptor can be determined in virologically suppressed patients, thus allowing MVC to be used as a switch option. This testing platform is tentatively endorsed by the German/Austrian (http://www.daignet.de/site-content/hiv-therapie/leitlinien-1) and European guidelines [12], but with a weak evidence base.

The Maraviroc Switch (MARCH) study aimed to define whether, in HIV-1–infected adults on a stable 2-N(t)RTI + ritonavir-boosted protease inhibitor (PI/r) cART regimen and with R5 virus as determined by proviral DNA tropism testing, replacing either the PI/r or 2 N(t)RTIs with MVC provided noninferior virological efficacy and improvements in safety and tolerability relative to remaining on a 2-N(t)RTI + PI/r regimen.

METHODS

Study Design

MARCH is an international, multicenter, randomized (1:2:2), open-label, 96-week noninferiority switch study of MVC 300 mg twice daily with a 2-N(t)RTI backbone vs MVC 150 mg twice daily (recommended dosing in the presence of a pharmacokinetic enhancer [http://www.selzentry.com]) with a PI/r vs continuing the current 2-N(t)RTI + PI/r (control) regimen.

Study Population

Participants were included if they were HIV-1–infected adults aged ≥18 years, with plasma HIV RNA (viral load [VL]) <200 copies/mL on a stable (>24 weeks) 2-N(t)RTI + PI/r regimen. Participants were excluded if they were pregnant or breastfeeding, had known genotypic resistance and/or prior virological failure/rebound, had an anticipated need to modify current cART for toxicity in the next 6 months, or had active hepatitis B coinfection, or if specific hematological/biochemical parameters were outside protocol-specified ranges. Other exclusions included use of medications contraindicated with MVC, acute therapy for serious infection/medical illness, use of immunomodulators ≤30 days prior to enrollment, current alcohol/illicit substance use that would conflict with study conduct, or compulsorily detained. The protocol and patient information statement and consent form were approved by the ethics committee/institutional review board at all participating sites. Written informed consent was obtained from all participants.

Proviral DNA Tropism Testing for Eligibility

For population tropism genotyping, several in-house protocols have been optimized and cover most subtypes and circulating recombinant forms [13–15]. Overall, the interpretation of the V3 sequence is via algorithms that predict the likelihood of co-receptor usage—for example, geno2pheno (http://www.geno2pheno.org). For MARCH study eligibility, participants were deemed to have R5 virus if each of the 3 sequences of the relevant portion of the V3 loop had a false-positive rate of ≥10% using the standard geno2pheno algorithm or if 2 of 3 sequences were R5 and 1 sequence failed to amplify. A single repeat sample could be drawn in the case of test failure. In this circumstance, the patient's virus was declared R5 if there were ≥3 R5 sequences and no X4 from both samples. Tropism testing was conducted at 14 certified laboratories [16], each using its own laboratory procedures.

Assessments

A computer-generated randomization sequence with a blocking factor of 5, stratified by site, was created by the study statistician. Eligible participants were randomly assigned through an electronic case report form. At the time of sample size reduction (see below), arm allocation was changed to using a minimization strategy (www.sghms.ac.uk/depts/phs/guide/randser.htm) to reduce the risk of imbalance between arms.

Eligible participants were randomized ≤60 days of screening and seen subsequently at weeks 4, 12, and every 12 weeks thereafter until week 96. At each study visit vital signs, targeted physical examination, changes in randomly assigned therapy and concomitant medications, adverse events (AEs), HIV-1 RNA with a lower limit of detection of at least <200 copies/mL at the local laboratories, T-cell enumeration, and safety laboratory tests (biochemistry/hematology/pregnancy) were collected. Fasting (≥8 hours) lipid and glycemic parameters were performed at all visits (except week 36) in year 1 and annually thereafter. Annual assessments in all patients included anthropometric measurements, bone mineral density (BMD), and peripheral and central fat using dual-energy X-ray absorptiometry (DXA) scanning and quality of life (QoL) using the 12-Item Short-Form Health Survey (SF-12) instrument. ART adherence was assessed at weeks 4, 48, and 96 using a validated self-reporting 7-day recall adherence tool [17]. Plasma and sera were collected at each study visit; plasma and a buffy coat were

taken for central genotypic resistance testing (protease and reverse transcriptase sequencing) and genotypic tropism testing in those with confirmed virological failure (defined below).

Endpoints

The primary endpoint was the comparison of proportions of participants with HIV RNA <200 copies/mL 48 weeks after randomization between control and each switch arm. Secondary endpoints included difference between control and switch arms over 48 weeks as follows. Virologic: proportion with plasma HIV RNA <50 copies/mL; time to virological failure defined as plasma HIV RNA ≥200 copies/mL on randomized therapy, on 2 occasions ≥7 days apart; time to loss of virological response defined by virological failure, permanent discontinuation of randomized treatment, new AIDS-defining illness, death, or withdrawal from the study; change in plasma HIV RNA $\log_{10}$ copies/mL; frequency of plasma virus "blips" (nonsustained VL >200 copies/mL); genotypic resistance at virological failure. Immunologic: changes from baseline in $CD4^+$ T-cell count (absolute and percentage). Clinical: rates of opportunistic disease, serious non-AIDS-defining illness, and non-AIDS-related mortality. Metabolic and body composition: changes from baseline in fasting lipids (total cholesterol, low-density lipoprotein cholesterol [LDL-c], high-density lipoprotein cholesterol, triglycerides), fasting glucose, and insulin; absolute 10-year CVD risk assessment using the Framingham risk score (http://cvdrisk.nhlbi.nih.gov); rates of initiation/changes in existing lipid-lowering therapies; changes from baseline in body fat and BMD derived from DXA; changes in 10-year fracture risk (FRAX algorithm) and bone turnover markers. Safety: changes from baseline in selected serum biochemical parameters, including estimated glomerular filtration rate (GFR); proportions experiencing and types of serious adverse events (SAEs); proportions experiencing AEs, and types and severity of AEs. Adherence: self-reported at weeks 4 and 48. QoL: change from baseline health status scores using the SF-12 health status.

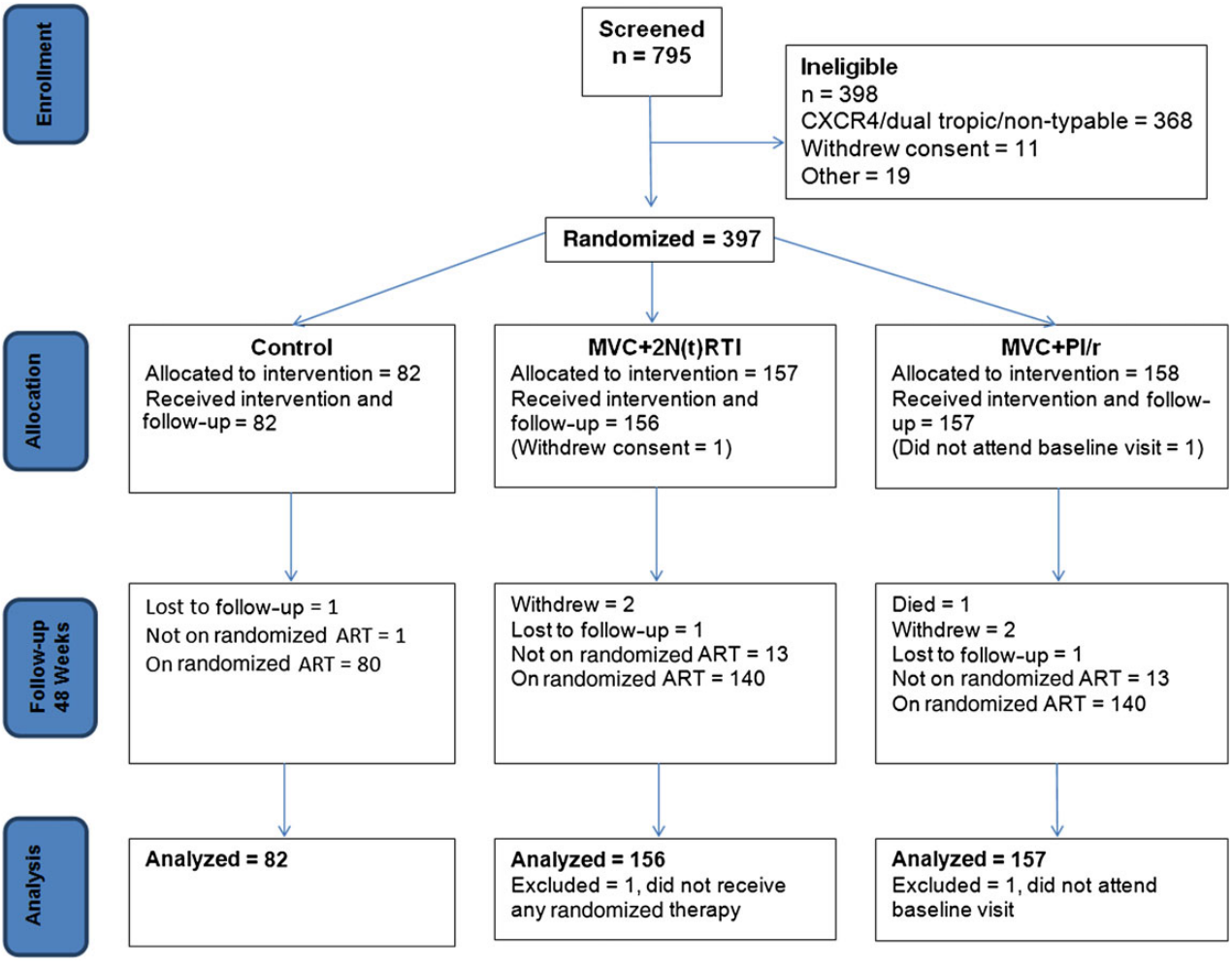

Figure 1. Maraviroc Switch Study recruitment and participant disposition. Abbreviations: ART, antiretroviral therapy; MVC, maraviroc; N(t)RTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI/r, ritonavir-boosted protease inhibitor.

Statistical Analysis

In May 2013, the sample size was reduced to 380 (from the original 560) participants randomized 1:2:2 (76:152:152) to control; MVC + 2 N(t)RTIs; MVC + PI/r. This was in response to the slower than expected enrollment. The sample size reduction resulted in a loss of power from 90% to 80% to demonstrate virological noninferiority of the switch arms vs control.

Treatment was to continue until the last randomized participant completed 96 weeks of follow-up or had permanently withdrawn from follow-up. The criteria by which the experimental switch regimens were judged noninferior to the control regimen was if the lower limit of the 95% confidence interval (CI) for the difference in virological response between each experimental arm and the control arm did not extend below −12%. Tests for noninferiority were primarily performed in the intention-to-treat (ITT) study population. A supportive analysis of the per-protocol (PP) population was also pre-planned. For secondary and exploratory efficacy endpoints, the ITT population was primary, followed by the PP population. Safety data were analyzed by randomized arm on available data. All comparisons were pairwise between an experimental arm and the control arm. All differences were experimental arm minus control arm. The χ^2 test, or where cell sizes were less than Fisher exact test, were used to compare proportions–tests for means and Cox proportional hazards for incidence rates. All statistical tests were 2-sided and considered significant at $\alpha < .05$. Statistical analyses were performed using SAS version 9.4 and Stata 13 software.

RESULTS

Study Status

The first and last randomizations were 19 January 2012 and 12 February 2014, respectively. All participants completed 48 weeks of follow-up by 14 January 2015. The data for this analysis were extracted on 6 February 2015. Participant follow-up is ongoing.

Participant Disposition

Seven hundred ninety-five participants were screened from sites in 13 countries (Argentina, Australia, Canada, Chile, France, Germany, Ireland, Japan, Mexico, Poland, Spain, Thailand, United Kingdom). Disposition and analysis populations are described in greater detail in Figure 1. The ITT population comprised 395 participants who commenced randomized therapy, attended baseline, and had ≥1 study visit.

Baseline Characteristics

Baseline characteristics were well balanced across the arms (Table 1). Twenty-three percent of participants were women; the mean age was 43 years; 56% and 32% were of white and Hispanic/Latino ethnicity, respectively. Sixty percent had category A disease; 96% had plasma VL <50 copies/mL; the mean $CD4^+$ T-cell count was 617 cells/μL, and the mean ART duration was 6.1 years. Sixty-eight percent were on tenofovir-based N(t)RTI backbones; 35%, 28%, and 17% were on ritonavir-boosted atazanavir, lopinavir (LPV/r), or darunavir, respectively (Table 2). Overall, the types of N(t)RTI backbone were similar across

Table 1. Maraviroc Switch Study Baseline Characteristics

Characteristic	Control (n = 82)[a]	MVC + 2 N(t)RTIs (n = 156)[a]	MVC + PI/r (n = 157)[a]	Total (N = 395)[a]
Female, No. (%)	20 (24.4)	35 (22.4)	35 (22.3)	90 (22.8)
Age, y, mean (SD)	43.6 (10.5)	43.7 (10.5)	42.7 (9.6)	43.3 (10.1)
Ethnicity, No. (%)				
African heritage	0 (0.0)	6 (3.9)	4 (2.6)	10 (2.5)
Asian	9 (11.0)	10 (6.4)	15 (9.6)	34 (8.6)
Australian Aboriginal	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
White	42 (51.2)	99 (63.5)	80 (51.0)	221 (56.0)
Hispanic or Latino	31 (37.8)	40 (25.6)	56 (35.7)	127 (32.2)
Other	0 (0.0)	1 (0.6)	1 (0.6)	2 (0.5)
CDC category C, No. (%)	21 (25.6)	36 (23.1)	30 (19.1)	87 (22.0)
Baseline HIV RNA <50 copies/mL	96.3%	96.8%	95.5%	96.2%
$CD4^+$ T cells/μL, mean (SD)	634.8 (244.5)	596.3 (253.3)	637.6 (252.7)	617.0 (251.2)
Nadir $CD4^+$ T cells/μL, mean (SD)	258 (169)	206 (156)	238 (143)	213 (162)
ART duration, y, mean (SD)	6.3 (4.5)	5.7 (3.8)	6.4 (4.4)	6.1 (4.2)
GFR, mL/min, mean (SD)	99.39 (20.59)	106.61 (71.77) (n = 155)	100.73 (22.37)	102.77 (48.11) (n = 394)
Total cholesterol, mmol/L, mean (SD)	4.87 (1.1) (n = 79)	4.89 (1.04) (n = 146)	4.89 (1.01) (n = 155)	4.89 (1.04) (n = 380)
LDL-c, mmol/L, mean (SD)	2.82 (0.96) (n = 79)	2.87 (0.86) (n = 142)	2.86 (0.94) (n = 150)	2.86 (0.91) (n = 371)
HDL-c, mmol/L, mean (SD)	1.21 (0.29) (n = 79)	1.26 (0.39) (n = 146)	1.26 (0.41) (n = 155)	1.25 (0.38) (n = 380)
TGs, mmol/L, mean (SD)	1.91 (0.99) (n = 79)	1.77 (0.93) (n = 144)	1.98 (1.4) (n = 152)	1.88 (1.16) (n = 375)
Right hip T-score, mean (SD)	−0.3 (1.28) (n = 76)	−0.71 (1.1) (n = 131)	−0.6 (1.04) (n = 143)	−0.58 (1.13) (n = 350)
Lumbar (T2–T4) T-score, mean (SD)	−0.75 (1.23) (n = 77)	−1.24 (1.35) (n = 134)	−1.18 (1.27) (n = 143)	−1.11 (1.3) (n = 354)

Abbreviations: ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; GFR, glomerular filtration rate; HDL-c, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; LDL-c, low-density lipoprotein cholesterol; MVC, maraviroc; N(t)RTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI/r, ritonavir-boosted protease inhibitor; SD, standard deviation; TGs, triglycerides;

[a] If data are available for fewer participants, this will be indicated in brackets against each baseline characteristic.

Table 2. Maraviroc Switch Study Baseline Antiretroviral Therapy

Characteristic	Control (n = 82)	MVC + 2 N(t) RTIs (n = 156)	MVC + PI/r (n = 157)	Total (N = 395)
N(t)RTI				
TDF/FTC	38 (46.3)	82 (52.6)	83 (52.9)	203 (51.4)
TDF/3TC	13 (15.9)	26 (16.7)	25 (15.9)	64 (16.2)
ABC/3TC	18 (22.0)	19 (12.2)	20 (12.7)	57 (14.4)
ZDV/3TC	6 (7.3)	20 (12.8)	17 (10.8)	43 (10.9)
Other	7 (8.5)	9 (5.6)	12 (7.6)	28 (7.1)
PI/r				
ATV/r	27 (32.9)	58 (37.2)	55 (35.0)	140 (35.4)
LPV/r	29 (35.4)	33 (21.2)	50 (31.9)	112 (28.4)
DRV/r	13 (15.9)	32 (20.5)	20 (12.7)	65 (16.5)
SQV/r	9 (11.0)	24 (15.4)	22 (14.0)	55 (13.92)
FPV/r	4 (4.9)	8 (5.1)	10 (6.4)	22 (5.6)
IDV/r	0 (0.0)	1 (0.6)	0 (0.00)	1 (0.3)

Data are presented as No. (%).

Abbreviations: 3TC, lamivudine; ABC, abacavir; ATV/r, ritonavir-boosted atazanavir; DRV/r, ritonavir-boosted darunavir; FPV/r, ritonavir-boosted fosamprenavir; FTC, emtricitabine; IDV/r, ritonavir-boosted indinavir; LPV/r, ritonavir-boosted lopinavir; MVC, maraviroc; N(t)RTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI/r, ritonavir-boosted protease inhibitor; SQV/r, ritonavir-boosted saquinavir; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine.

arms; however, abacavir/lamivudine was used in 22% of the control arm vs 12% and 13% of the MVC + 2 N(t)RTI and MVC + PI/r arms, respectively. The most common PI/r was ritonavir-boosted atazanavir, then LPV/r in all 3 arms. LPV/r was the PI/r used in 21% of the MVC + 2 N(t)RTI arm, compared with 35% and 32% in the control and MVC + PI/r arms, respectively. Mean Framingham 10-year CVD risk (available in 377 participants) was 6.64% (standard deviation [SD], 6.16%): 6.87% (SD, 7.21%) in the control (n = 78), 6.3% (SD, 5.56%) in the MVC + 2 N(t)RTI (n = 144), and 6.84% (SD, 6.15%) in the MVC + PI/r (n = 155) arms. The mean T-score at the lumbar spine site only (Table 1) showed mild osteopenia in all 3 arms.

Primary Endpoint and Other Major Secondary Outcomes

The N(t)RTI-sparing regimen of MVC + PI/r did not meet noninferiority criteria and was significantly inferior to the control arm in the ITT analysis (Table 3). In contrast, high rates of virological suppression (<200 copies/mL and <50 copies/mL) were maintained in those on the control arm and those switching to MVC + 2 N(t)RTIs. Time to loss of virological suppression to <200 copies/mL and <50 copies/mL is shown in Figures 2 and 3, respectively. Loss of virological suppression began early (within the first 24 weeks) after the randomized switch in those on the N(t)RTI-sparing regimen. The hazard ratio for loss of virological response <200 copies/mL and <50 copies/mL over 48 weeks, respectively, was 2.41 (95% CI, 1.31–4.43; $P = .005$) and 2.16 (95% CI, 1.34–3.48; $P = .001$), respectively, for the MVC + PI/r arm vs control arm. No formal analysis of patient-reported adherence at weeks 4 and 48 was performed, as only 1.3% reported taking approximately half or less of their ART. Week 4 and week 48 seven-day recall adherence was available for 97% and 96% of the ITT population, respectively; of these, 88% (week 4) and 90% (week 48) reported taking all of their ART, and 10% (week 4) and 8% (week 48) reported taking most of their ART. There was no difference in 7-day recall between the switch arms. Eleven participants ceased randomized therapy for high VL; of these 0, 5, and 6 were in

Table 3. Maraviroc Switch Study Virological Outcomes: 48-Week Data

Analysis	Arm	Below Threshold, %	Difference, %	(95% CI)
Intention to treat				
<50 copies/mL	Control	95.1	Reference	
	MVC + 2 N(t)RTIs	91.7	−3.5	(−9.6 to 3.8)
	MVC + PI/r	77.7	−17.4	(−24.9 to −8.4)
<200 copies/mL	Control	97.6	Reference	
	MVC + 2 N(t)RTIs	93.6	−4.0	(−9.0 to 2.2)
	MVC + PI/r	84.1	−13.5	(−19.8 to −5.8)
Noncompletion = failure				
<50 copies/mL	Control	93.9	Reference	
	MVC + 2 N(t)RTIs	87.2	−6.7	(−13.8 to 1.5)
	MVC + PI/r	74.5	−19.4	(−27.4 to −9.9)
<200 copies/mL	Control	96.3	Reference	
	MVC + 2 N(t)RTIs	88.5	−7.9	(−14.1 to −.4)
	MVC + PI/r	80.3	−16.1	(−23.1 to −7.6)
Per-protocol				
<50 copies/mL	Control	96.3	Reference	
	MVC + 2 N(t)RTIs	97.1	0.9	(−4.2 to 6.9)
	MVC + PI/r	83.6	−12.7	(−19.8 to −4.3)
<200 copies/mL	Control	98.8	Reference	
	MVC + 2 N(t)RTIs	98.6	−0.2	(−3.8 to 4.4)
	MVC + PI/r	90	−8.8	(−14.2 to −2.1)

Abbreviations: CI, confidence interval; MVC, maraviroc; N(t)RTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI/r, ritonavir-boosted protease inhibitor.

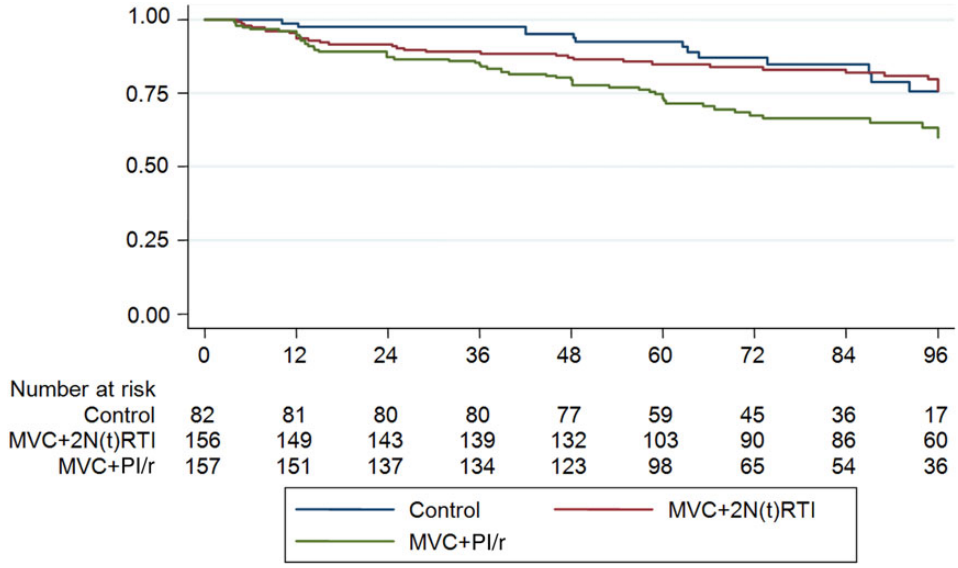

Figure 2. Proportion of participants with virologic response (<200 copies/mL), by week. Abbreviations: MVC, maraviroc; N(t)RTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI/r, ritonavir-boosted protease inhibitor.

the control, MVC + 2 N(t)RTI, and MVC + PI/r arms, respectively. Up to week 48, there were 18 confirmed VL "blips" in 17 individuals, 13 of which (72%) occurred in the MVC + PI/r arm.

Changes in Immunological and Metabolic Parameters and Quality of Life Over 48 Weeks

$CD4^+$ T cells increased 40, 39, and 29 cells/μL in the control, MVC + 2 N(t)RTI, and MVC + PI/r arms, respectively, from baseline. There was a significant decrease in both the mean total (−0.45 mmol/L; $P < .0001$) and LDL-c (−0.27 mmol/L; $P \leq .0002$) in patients switching to the MVC + 2 N(t)RTI arm compared with control (Table 4), but these declines did not translate into a significant change in Framingham 10-year CVD risk score. Of the available BMD change data (70, 123, and 127 in the control, MVC + 2 N(t)RTI, and MVC + PI/r arms, respectively), the T-score at the lumbar spine declined a

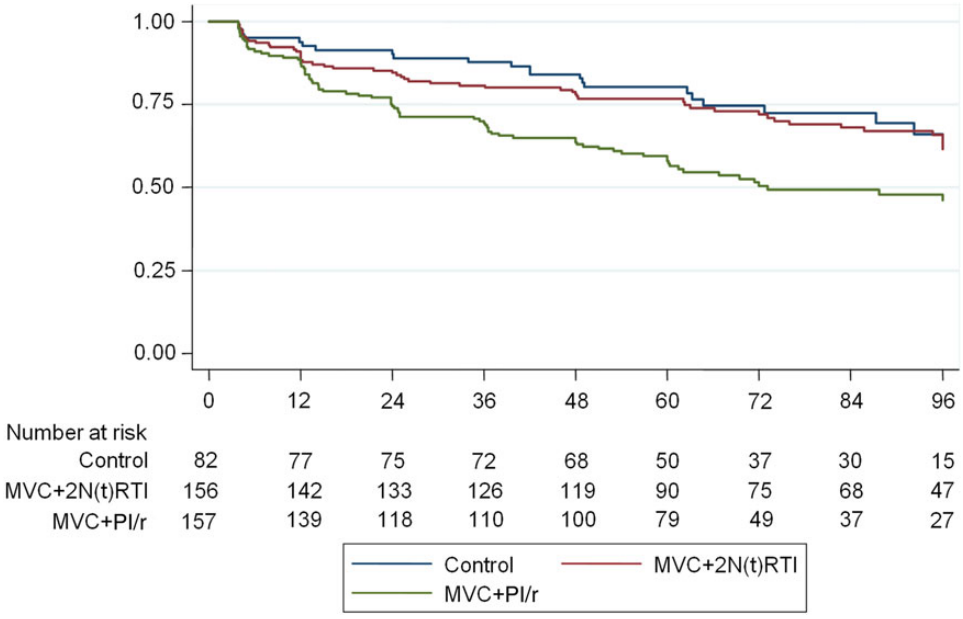

Figure 3. Proportion of participants with virologic response (<50 copies/mL), by week. Abbreviations: MVC, maraviroc; N(t)RTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI/r, ritonavir-boosted protease inhibitor.

Table 4. Changes in Lipid Parameters

Characteristic	Arm	No.	Mean	(95% CI)	*P* Value
Total cholesterol (mmol/L)	Control	77	0.06	(−.15 to .28)	
	MVC + 2 N(t)RTIs	134	−0.45	(−.59 to −.31)	<.0001
	Difference		0.51	(.26–.76)	
	MVC + PI/r	150	0.34	(.19–.48)	
	Difference		−0.27	(−.53 to −.02)	.0345
HDL-c (mmol/L)	Control	77	0.05	(.00–.11)	
	MVC + 2 N(t)RTIs	134	0.04	(−.01 to .08)	
	Difference		0.02	(−.06 to .09)	.628
	MVC + PI/r	150	0.10	(.04–.16)	
	Difference		−0.04	(−.14 to .05)	.3591
LDL-c (mmol/L)	Control	77	0.10	(−.08 to .28)	
	MVC + 2 N(t)RTIs	132	−0.27	(−.38 to −.16)	
	Difference		0.37	(.17–.57)	.0002
	MVC + PI/r	143	0.18	(.05–.30)	
	Difference		−0.07	(−.29 to .14)	.4871
TGs (mmol/L)	Control	77	−0.0795	(−.2816 to .1227)	
	MVC + 2 N(t)RTIs	134	−0.4016	(−.5418 to −.2615)	
	Difference		0.3222	(.0835–.5608)	.0084
	MVC + PI/r	147	0.1146	(−.1857 to .4148)	
	Difference		−0.194	(−.6326 to .2445)	.3842

Abbreviations: CI, confidence interval; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; MVC, maraviroc; N(t)RTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI/r, ritonavir-boosted protease inhibitor; TGs, triglycerides.

mean of −0.05 (95% CI, −.12 to .02) in the control arm vs a gain of 0.08 (95% CI, −.00 to .16) in the MVC + 2 N(t)RTI arm ($P = .03$ vs control) and a gain of 0.10 (95% CI, .04–.17) in the MVC + PI/r arm ($P = .0028$ vs control). At the right hip, T-score changes in control vs the MVC + 2 N(t)RTI arm were nonsignificant: −0.12 (95% CI, −.12 to .02) and −0.12 (95% CI, −.25 to .01), respectively ($P = .069$). Participants in the N(t)RTI-sparing arm had a mean positive T-score gain at the right hip of 0.07 (95% CI, −.01 to .16; $P = .01$) vs the control arm. In comparing the control to each switch arm, there were no significant percentage changes in physical or mental QoL domains.

Safety Findings at 48 Weeks

Eight hundred eighty-four AEs were reported; 86% were determined as not related or probably not related to study drugs. There was no hepatic safety signal. Mean changes in GFR (mL/minute) were nonsignificant, with mean changes of −1.96 (95% CI, −6.11 to 2.19), −9.54 (95% CI, −20.89 to 1.80), and −0.69 (95% CI, −3.61 to 2.24) in the control, MVC + 2 N(t)RTI, and MVC + PI/r arms, respectively. Up to week 48, 35 participants (2 in the control, 16 in the MVC + 2 N(t)RTI, and 17 in the MVC + PI/r arms) ceased randomized therapy; in 6 participants (1, 4, and 1 in the control, MVC + 2 N(t)RTI, and MVC + PI/r arms, respectively), an AE was the reason given for stopping randomized therapy. Thirty-seven SAEs occurred; 8 (9.76% of the control arm), 15 (9.62% of the MVC + 2 N(t)RTI arm), and 14 (8.92% MVC + PI/r arm) events. During the 48 weeks of follow-up, 1 patient died, 1 patient in the MVC + PI/r arm developed an AIDS-defining illness (multidermatomal herpes zoster), and 9 had serious non-AIDS-defining events (2 and 7 in the control and MVC arms, respectively). One myocardial infarction event was reported as a safety alert in a patient on MVC. Of note, this patient's lifestyle and cardiac congenital malformation placed them at increased CVD risk.

Resistance

Twenty-five participants (1, 6, and 18 in the control, MVC + 2 N(t)RTI, and MVC + PI/r arms, respectively) had confirmed virological failure during 48 weeks of follow-up. As shown in Table 5, sequencing was successful in 23 of 25 (median VL, 2280 copies/mL); repeat tropism testing (phenotypic testing as a DNA sample was not available in all) [18] was successful in 18 of the 25 participants. The majority of patients had virological failure without any emergent major mutations in the protease or reverse transcriptase (15 of 23 [65%]); 15 of 18 (83%) samples with a repeat tropism remained R5-tropic. Major protease mutations were found in 2 participants, L90M in one and I50V in the other. Surprisingly, 4 participants (1, 2, and 1 in the control, MVC + 2 N(t)RTI, and MVC + PI/r arms, respectively) had emergent major nonnucleoside reverse transcriptase inhibitor (NNRTI) mutations; in 3 of these, repeat tropism confirmed R5-tropic virus.

DISCUSSION

This is the largest randomized study using genotypic assessment of virus tropism using HIV DNA to determine the likelihood of MVC activity in a switch setting. The findings strengthen the

Table 5. Emergent Resistance in Maraviroc Switch Study Participants With Confirmed Virological Failure Over 48 Weeks

Study Arm	Confirmed Virological Failure	Viral Load at Viral Failure, Copies/mL	Country of Enrollment	PI and RT Sequencing Results	Tropism (Phenotypic Assessment) at Viral Failure
Control	Week 36	2280.0	Argentina	**K103KN**	CCR5
MVC + 2 N(t)RTIs	Week 12	7248.0	Argentina	**M41L, T215E**	CCR5
MVC + 2 N(t)RTIs	Week 12	55 808.0	Mexico	**M184V, K101E, Y181C, G190A**	CCR5
MVC + 2 N(t)RTIs	Week 12	2810.0	Germany	L10I, **K65R; V106I**	Test failed
MVC + 2 N(t)RTIs	Week 36	4812.0	Spain	L10I, A71V, **M184V**	CCR5
MVC + 2 N(t)RTIs	Week 12	1133.0	Poland	**L90M,** L10I, A71V, **M184MV**	CCR5
MVC + PI/r	Week 48	891.0	Argentina	None	CCR5
MVC + PI/r	Week 48	730.0	Argentina	L10I	Test failed
MVC + PI/r	Week 24	60 800.0	Argentina	**I50V,** L10I, L33FL	CXCR4
MVC + PI/r	Week 4	30 600.0	Argentina	None	CCR5
MVC + PI/r	Week 36	111 941.0	Chile	None	CXCR4
MVC + PI/r	Week 12	1157.0	Mexico	None	CCR5
MVC + PI/r	Week 36	5565.0	Mexico	A62V, **T215S**	CCR5
MVC + PI/r	Week 48	63 140.0	Mexico	None	CXCR4
MVC + PI/r	Week 48	5935.0	Canada	None	CCR5
MVC + PI/r	Week 36	1200.0	Germany	K20I	Test failed
MVC + PI/r	Week 12	2208.0	Germany	None	CCR5
MVC + PI/r	Week 12	45 600.0	Germany	None	CCR5
MVC + PI/r	Week 12	2275.0	Germany	E138A	CCR5
MVC + PI/r	Week 12	545.0	Poland	V32AV	Test failed
MVC + PI/r	Week 12	1924.0	Poland	None	Test failed
MVC + PI/r	Week 36	2264.0	Poland	None	CCR5
MVC + PI/r	Week 48	821.0	Poland	L10I	CCR5

Mutations highlighted in bold are major mutations of PI and RT (nucleoside reverse transcriptase inhibitor and nonnucleoside reverse transcriptase inhibitor).

Abbreviations: MVC, maraviroc; N(t)RTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; PI/r, ritonavir-boosted protease inhibitor; RT, reverse transcriptase.

evidence base for this testing platform at the cutoffs used. Just under 50% of those screened were ineligible because virus tropism was determined as X4/dual tropic or nonclassifiable. This international study had a novel design for a switch study, separating the "traditional" components of a PI/r-based regimen to test the contribution of each component to virological control, metabolic changes, and side effects. MVC represented an attractive switch choice as it is potent and well tolerated, with neutral impacts on lipids and renal function. Somewhat surprisingly, the N(t)RTI-sparing arm was significantly inferior in regard to virological control compared with the control arm over 48 weeks of follow-up. This excess loss of virological control was not explained by reduced adherence as measured in the study. In contrast, those randomized to MVC in lieu of their PI/r and remaining on their original 2-N(t)RTI backbone retained high rates of virological suppression similar to those remaining on their original regimen of PI/r + 2 N(t)RTIs. These data suggest that a PI/r is not an effective "backbone" for MVC in the switch/simplification setting. These unexpected findings highlight the importance of randomized trials of this nature. The findings are in line with findings from some other N(t)RTI-sparing studies [19], including one that combined MVC with raltegravir [20], and suggest that specific inhibition of reverse transcriptase may be more important than previously thought.

One of the rationales for performing switch studies is to test other benefits including side effects, tolerability, renal safety, metabolic changes, and immunological benefits. In this switch study, MVC was confirmed as safe and well tolerated. The study confirms the neutral impact of MVC on renal function. There were potentially beneficial changes in lipids in those switching away from PI/r, but these changes, while important, did not translate into a significant change in the 10-year cardiovascular risk using the Framingham equation over the relatively short period of follow-up. In the longer term, these lipid changes may have a positive impact on reducing cardiovascular risk. There were also significant, albeit small improvements in lumbar spine BMD in both MVC switch arms and at the right hip in the MVC + PI/r switch arm.

All 3 arms showed $CD4^+$ T-cell gains over 48 weeks of follow-up, this despite the patients already being on cART for a median of just over 6 years. However, in those switching to MVC, $CD4^+$ T-cell gain was not enhanced compared to the control arm. $CD8^+$ T cells increased significantly over the 48 weeks (data not shown) in the MVC arms. The clinical significance of this is unknown, but confirms previous findings and is thought to be an effect on T-cell trafficking via CCR5 blockade [21].

Although rates of both confirmed virological failure and virological blipping were significantly higher in the N(t)RTI-sparing

arm, in those who could be sequenced, only 2 patients had an emergent major PI mutation, suggesting that virological failure in this setting would not result in loss of future treatment options with a PI/r-based regimen for the majority of patients. The relatively high rates of emergent NNRTI resistance suggest that patients with transmitted NNRTI resistance or prior NNRTI failure were enrolled in the study, something we tried to avoid when designing the exclusions for study participation. Importantly, most participants appeared to retain R5-tropic virus, so the reasons for virological failure could not be ascribed to emergent X4-tropic virus, at least using the clinical cutoffs we applied. In addition, 30% of participants with virological failure had no emergent protease or reverse transcriptase mutations and their virus remained R5-tropic, suggesting that poor adherence—not detected through the 7-day recall at weeks 4 and 48—might have contributed to viral failure.

In summary, this large international randomized study demonstrates that MVC with a 2-N(t)RTI backbone, in those with R5-tropic virus determined by genotypic tropism testing, is a switch/simplification option for patients virologically suppressed on PI/r–N(t)RTI regimens. MVC was safe and well tolerated, with favorable impact on lipids and neutral effects on renal function over 48 weeks.

Notes

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APPENDIX

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