Virologic Response, Early HIV-1 Decay, and Maraviroc Pharmacokinetics With the Nucleos(t)ide-Free Regimen of MaravIroc Plus Darunavir/Ritonavir in a Pilot Study

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Objective: To address the need for nucleos(t)ide reverse transcriptase inhibitor (NRTI)–sparing regimens, we explored the virologic and pharmacokinetic characteristics of maraviroc plus ritonavir-boosted darunavir in a single-arm, open-label, 96-week study.

Methods: Twenty-four antiretroviral-naive R5 HIV-1–infected participants received maraviroc 150 mg and darunavir/ritonavir (DRV/r) 800/100 mg (MVC/DRV/r) once daily. The primary outcome was virologic failure (VF) = confirmed viral load (VL) >50 copies per milliliter at week 24 in the modified intent-to-treat population. To determine viral dynamics, participant-specific first- and second-phase empirical Bayes estimates were compared with decay rates from efavirenz (EFV) plus lopinavir/ritonavir, lopinavir/ritonavir plus 2NRTIs, and EFV plus 2NRTIs. Maraviroc plasma concentrations were determined at weeks 2, 4, 12, 24, and 48.

Results: Baseline median (Q1, Q3) CD4 count and VL were 455 (299, 607) cells per cubic millimeter and 4.62 (4.18, 4.80) $\log_{10}$ copies per milliliter, respectively. VF occurred in 3 of 24 participants {12.5% [95% confidence interval (CI): 2.7 to 32.4]} at week 24. One of these resuppressed, yielding a week 48 VF rate of 2/24 [8.3% (95% CI: 1.0 to 27.0)]. The week 48 failures were 2 of the 4 participants (50%) with baseline VL >100,000 copies per milliliter. Week 96 VF rate was 2/20 [10% (95% CI: 1.2 to 31.7)]. Phase 1 decay was faster with MVC/DRV/r than reported for ritonavir-boosted lopinavir plus 2NRTIs ($P = 0.0063$) and similar to EFV-based regimens. Individual maraviroc trough concentrations collected between 20 and 28 hours post dose (n = 59) was 13.7 to 130 ng/mL (Q_1, 23.4 ng/mL; Q_3, 46.5 ng/mL), and modeled steady-state concentration was 128 ng/mL.

Conclusions: MVC/DRV/r 150/800/100 mg once daily has potential for treatment-naive patients with R5 HIV-1.

Key Words: maraviroc, darunavir, nucleos(t)ide sparing, pharmacokinetics, viral dynamics

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INTRODUCTION

Although several nucleos(t)ide reverse transcriptase inhibitor (NRTI)–sparing regimens have been investigated for initial treatment of HIV,[1–4] all recommended regimens worldwide include 2NRTIs.[5–9] Effective NRTI-sparing regimens would provide options for individuals with transmitted NRTI resistance and renal impairment and avoid long-term NRTI toxicities.[10] Maraviroc (MVC) is a CCR5 receptor antagonist with activity against R5 HIV-1 and possible though unproven immunomodulatory properties.[11–13] Darunavir (DRV) is a protease inhibitor (PI) with a high barrier against resistance.[14] Both MVC and ritonavir-boosted DRV (DRV/r) have reliable cerebrospinal

fluid penetration,[15,16] rare serious toxicities,[15,17] and are associated with robust CD4+ T (CD4)–cell reconstitution.[18,19]

The recommended MVC dose when combined with NRTIs is 300 mg twice daily.[5] Among treatment-naive patients randomized to MVC 300 mg plus lamivudine/zidovudine twice daily in the MERIT study, the probability of virologic success decreased when average MVC plasma concentration (C_{avg}) and trough concentrations (C_{trough}) fell below 75 and 25 ng/mL, respectively.[20] DRV/r inhibits cytochrome P450 (CYP) 3A4–mediated metabolism of MVC, resulting in a 4-fold increase in MVC area under the plasma concentration–time curve.[11,21] The recommended MVC dose when coadministered with DRV/r is 150 mg twice daily.[5] However, half of the recommended dose (150 mg once daily) combined with DRV/r 800/100 mg daily produced median interquartile ratio MVC C_{trough} of 43 ng/mL (35–55 ng/mL) in a clinical cohort.[22] In the MOTIVATE study, treatment-experienced patients were randomized to placebo, MVC 150 mg once daily, or MVC 150 mg twice daily combined with an optimized background regimen that included several investigator–chosen PIs but not darunavir.[23] At 48 weeks, plasma HIV-1 RNA concentration (viral load, VL) was <50 copies per milliliter in 179 of 414 participants (43%) and 194 of 426 participants (46%) on daily versus twice-daily MVC, respectively.

We conducted the single-arm MaravIroc plus DArunavir/ritonavir Study (MIDAS) [clinicalTrials.gov Identifier: NCT00993148] to explore whether once-daily MVC 150 mg plus DRV/r 800/100 mg (MVC/DRV/r) is an active NRTI-sparing regimen for initial treatment of R5 HIV-1. We also evaluated the early HIV-1 decay and MVC pharmacokinetics (PK) of this novel regimen.

MATERIALS AND METHODS

Study Participants

Participants were treatment-naive HIV-1–infected patients who were at least 18 years old with (1) VL of 5000 to 500,000 copies per milliliter within 90 days before study entry, (2) R5 virus by the enhanced sensitivity Trofile assay (Trofile ES), and (3) CD4 count >100 cells per cubic millimeter. We excluded patients with active hepatitis B, protocol-specified abnormal laboratory values, or any DRV resistance-associated mutation (V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V). Each participant was invited to participate in a viral dynamics substudy. Ethics review committees at each research site approved the study. Participants were provided a written informed consent. An independent Monitoring Committee reviewed the study after the first 15 patients reached week 12.

Study Intervention

Each participant received open-label DRV 800 mg (two 400 mg tablets), ritonavir 100 mg (1 capsule), and MVC 150 mg (1 tablet) coadministered once daily with food.

Procedures and Assessments

At the first screening visit, a Trofile ES assay on plasma was performed (Monogram, Inc., San Francisco, CA). Participants with only R5 virus returned for the second screening visit where other eligibility criteria were assessed. Study entry (day 0) occurred within 90 days of the first screening evaluation. Subsequent evaluations occurred at weeks 1, 2, 4, 12, 24, 36 48, 60, 72, 84, and 96. VL was determined at entry and all subsequent evaluation time points. Hematologic, liver function, and blood chemistry tests were performed at entry and weeks 2, 4, 12, 24, 36, 48, 60, 72, 84, and 96. CD4 count was determined at entry and weeks 12, 24, 36, 48, 60, 72, 84, and 96. Fasting lipid levels were measured at entry and weeks 24, 48, and 96. Participants in the viral dynamics substudy underwent additional VL determination on days 2, 4, and 10. Random samples for PK evaluation were collected, and an adherence questionnaire was administered at weeks 2, 4, 12, 24, and 48. Participants were classified as perfectly adherent if they reported taking study medications with food and had no missed doses in the preceding 4 days.[24] Participants with suspected virologic failure (VF) returned within 7–35 days for a failure confirmation visit where adherence was assessed and samples collected for VL, protease genotype, Trofile ES, MVC phenotypic assay, CD4 count, and PK evaluation.

VL was determined using the COBAS AmpliPrep/COBAS Taqman HIV-1 assay (Roche San Diego, CA). Resistance to PIs at the time of VF was assessed by genotyping the HIV-1 protease gene from plasma HIV-1 RNA. To isolate and sequence independent full-length env clones, viral RNA was extracted from patient plasma samples (QIAamp; Qiagen San Diego, CA). Independent env gp160 amplicons were generated by nested polymerase chain reaction as previously described.[25] Tropism and MVC resistance testing were done at time of VF.

Maraviroc Bioanalysis and PKs

A validated protein precipitation method using acetonitrile (AcN) containing internal standard (MVC-d6) was employed to extract MVC from human plasma. An aliquot of the supernatant was further diluted with 0.5% trifluoroacetic acid to maintain signal intensity within the linear range of the instrument. Reversed-phase chromatographic separation was performed on an XBridge C18 analytical column (2.1 × 50 mm, 3.5 mm) under isocratic conditions. A binary mobile phase consisting of 0.1% formic acid in water and 0.1% formic acid in acetonitrile (72:28) was used and provided adequate separation from other analytes in the assay. Detection and quantitation was achieved by multiple reaction monitoring, and MVC and internal standard (MVC-d6) were detected using the following transitions for protonated molecular products $[M + H]^+$: *m/z* MVC 514.2 → 106.0; *m/z* MVC-d6 520.3 → 115.0. The dynamic range was 5 to 5000 ng/mL using a 20 μL of plasma sample. PK modeling was conducted using ADAPT 5 (Biomedical Simulations Resource, Los Angeles, CA).[26] A 2-compartment model was utilized, and MVC absorption and clearance processes were assumed to be linear. Because few data points were available in the absorptive phase, the absorption rate constant (K_a) was fixed at 1.0 and no lag time was assessed. Covariates were not examined in this PK data set.

Outcome Measures

The primary outcome was VF (defined as confirmed plasma VL > 50 copies/mL) at week 24. Secondary outcome

measures were VF at weeks 48 and 96, change in CD4 count, adherence to study treatment, MVC PK, early viral decay, incidence of grade ≥3 or any grade if it led to drug discontinuation, change in viral tropism, or emergence of protease or MVC resistance.

Statistical Methods

With a sample size of 25 participants, assuming a 10% participant loss by week 24, if the observed VF rate was between 15% and 25%, then the 95% confidence interval (CI) would have a width of ±15% to ±18%. The 95% CI width was calculated using large sample approximation assuming a binomial distribution. Efficacy analysis was based on a modified intent-to-treat population, which included all participants who initiated MVC/DRV/r and censored participants at the time of loss to follow-up or treatment modification if the last VL was <50 copies per milliliter. VL <50 copies per milliliter while on MVC/DRV/r was considered a success. In secondary analysis, participants lost to follow-up or who had any treatment modification were considered failures.

Viral decay rates were estimated with a biexponential nonlinear mixed effects model using VL at days 0, 2, 4, 7, 10, 14, and 28 after initiating MVC/DRV/r. Models were fit to the data on a $\log_{10}$ scale to normalize the error distribution.[27] Participant-specific first- and second-phase empirical Bayes estimates were compared with decay rates from efavirenz (EFV) plus lopinavir/ritonavir (LPV/r), LPV/r plus 2NRTIs, and EFV plus 2NRTIs arms of ACTG A5160s[28] and EFV plus 2NRTIs arm of ACTG A5166s[29] using the primary data. We used a 2-sided Wilcoxon rank sum test unadjusted for multiple comparisons (A5160s and A5166s decay curves were determined from data through week 8). Models were also fit through week 12 to investigate bias of decay estimates in comparison to A5160s and A5166s because week 8 VLs were not collected with MVC/DRV/r. Viral decay models through week 4 are reported to eliminate bias from censoring undetectable VL values (0% through week 4 vs. 27% through week 12).

RESULTS

Study Participants

A total of 46 antiretroviral-naive HIV-1–infected volunteers underwent screening at 5 US research sites. Nine of these (20%) had non–R5 virus and 12 failed other eligibility criteria. Twenty-five participants with R5 HIV-1 enrolled in the study: median (Q1, Q3) age was 38 (31, 43) years, 88% were male, and 60% were white non-Hispanic. Baseline median CD4 count and VL were 455 (299, 607) cells per cubic millimeter and 4.62 (4.18, 4.80) $\log_{10}$ copies per milliliter, respectively. VL was >100,000 copies per milliliter in 4 participants (16%), 10,000–100,000 copies per milliliter in 16 participants (64%), and <10,000 copies per milliliter in 5 participants (20%). Baseline resistance mutations were detected in 5 participants (20%): 1 had PI (D30N) plus NRTI (L210W, M41L, T215C) mutations; 3 had nonnucleoside reverse transcriptase inhibitor (NNRTI) (K103N, Y181C) mutations only and 1 had NNRTI (Y181C) plus NRTI (M41L, T215D) mutations.

Virologic Response

One participant did not initiate MVC/DRV/r and was not included in the analysis. Twenty-four participants initiated MVC/DRV/r. All the participants with confirmed VL >50 copies per milliliter at or after week 24 are shown in Table 1. Participants A, B, and D experienced VF at week 24; VF rate = 3/24 [12.5% (95% CI: 2.7 to 32.4)]. All these participants remained on MVC and 1 (participant D) later resuppressed to VL <50 copies per milliliter. VF rate at week 48 was 2/24 [8.3 % (95% CI: 1.0 to 27.0)]. The week 48 failures were 2 of the 4 participants (50%) with baseline VL >100,000 copies per milliliter. All the 20 participants with baseline VL <100,000 copies per milliliter had VL <50 copies per milliliter at week 48. In secondary analysis considering participants lost to follow-up or who had any treatment modification as failures, VF rates at weeks 24 and 48 remained unchanged because none of the 24 participants who initiated MVC/DRV/r was lost to follow-up or had treatment modification through week 48.

To derive the week 96 VF rate, we censored 2 participants who were lost to follow-up after week 48 (at week 72 and week 84, respectively) while their VLs were <50 copies per milliliter on MVC/DRV/r (not shown in Table 1). In addition, we censored 2 other participants (A and C in Table 1) who switched from MVC/DRV/r while suppressed. Thus, the VFs at week 96 were participants B and E in Table 1, yielding a VF rate of 2/20 [10% (95% CI: 1.2 to 31.7)]. In secondary analysis considering participants lost to follow-up or who had any treatment modification as failures, VF at week 96 was 6/24 [25 % (95% CI: 9.7 to 46.7)]. All the subjects with VF reported perfect adherence at that time point, except patient E at week 96.

CD4 Response and Safety

Median (Q_1, Q_3) CD4 count change from baseline was +247 (119, 340) cells per cubic millimeter and +216 (119, 346) cells per cubic millimeter at weeks 48 and 96, respectively. The only grade 3 abnormality assessed as at least possibly related to the study regimen was low-density lipoprotein cholesterol elevation in 1 participant. There were no grade 4 adverse events or study discontinuations due to adverse events.

Resistance

None of the participants with VF had any baseline resistance mutation. We limited Trofile ES, protease genotyping, and phenotypic testing of MVC susceptibility to participants with VL >200 copies per milliliter after week 48 (patients A, B, and E in Table 1). HIV-1 tropism remained R5 in the 2 samples that were successfully tested. Genotypic and phenotypic DRV and MVC resistance testing could not be performed because HIV-1 pol and envelop amplification failed with different amplification strategies in all tested samples, most of which had too low plasma virus concentrations. To confirm RNA integrity, gag was successfully amplified from 1 of the 2 patients, suggesting that primer mismatch may also have played a role in our inability to amplify and sequence HIV-1 pol and envelope.

TABLE 1. Participants With Any VL >50 Copies Per Milliliter at or After Week 24*

	HIV RNA Copies Per Milliliter										
	Baseline	Week 2	Week 4	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96
A	277,373	3775	1951	219	82/67	119	78	249	89	<50	<50
B	156,013	1806	1320	365	224/496	247	257	268	1505/3826	<50	<50
C	166,567	1791	338	51	<50	94/98	<50	<50	<50	<50	<50
D	7903	438	204	<50	989/114	<50	<50	<50	<50	<50	<50
E	15,150	439	300	58	50	<50	<50	<50	139/<50	<50	1815/165

	Treatment Modification†	Tropism	Genotype	Maraviroc plasma concentration (time post dose)‡
A	TDF/FTC, DRV/r (after the week 84 visit)	NR (week 4)	Failed to amplify (week 60)	29.5 ng/mL (23 h) at week 24
B	EFV/TDF/FTC (at week 78)	R5 (week 4), NR (week 72)	Failed to amplify (week 72)	52.1 ng/mL (22 h) at week 24
C	EFV/TDF/FTC (after the week 48 visit)	ND	ND	Sampling ND at week 36
D	None	ND	ND	109.0 ng/mL (10 h) at week 24
E	None	R5 (week 96)	Failed to amplify (week 96)	167.5 ng/mL (9 h) at week 96

* All study participants remained on MVC/DRV/r through week 96 unless indicated in the treatment modification column. Some HIV RNA values are initial/confirmatory measurements at that time point.
† Participants A and C were switched before the VL results became available from weeks 84 and 48, respectively.
‡ Maraviroc trough concentration window is 20–28 hours post dose.
EFV/TDF/FTC, Atripla; ND, not done; NR, not reportable; TDF/FTC, Truvada.

Viral Dynamics

Fifteen participants enrolled in the viral dynamics substudy with median (Q_1, Q_3) pretreatment VL of 4.6 (4.2, 4.8) $\log_{10}$ copies per milliliter. As shown in Table 2, median phase 1 decay was faster with MVC/DRV/r than reported for LPV/r plus 2NRTIs.[28] The faster decay corresponded to a shorter median half-life (1.0 day vs. 1.3 days, respectively). The median phase 1 decay rate in this study was not significantly different from the phase 1 decay rates reported for EFV plus LPV/r or EFV plus 2NRTIs, respectively.[28,29] Median phase 2 decay with MVC/DRV/r was slower than reported for EFV plus LPV/r, LPV/r plus 2NRTIs, and EFV plus 2NRTIs, respectively, in A5160s,[28] and slower than the phase 2 decay rate reported for EFV plus 2NRTIs in A5166s.[29] Population average (fixed effects) biexponential decay in VL is shown in Figure 1. Because VL was not

TABLE 2. Phase 1 and Phase 2 HIV-1 RNA Decay Parameters of MIDAS Study (Through Week 4 or Week 12) Compared With Historical Controls Receiving EFV Plus LPV/r, LPV/r Plus 2NRTIs, and EFV Plus 2NRTIs in ACTG A5160s[28] and EFV Plus 2NRTIs in ACTG A5166s[29]

		Estimated Decay Parameter (Per Day)		
Regimen	n	Median (Q1, Q3)	Median Half-Life, d	*P**
Phase 1				
MIDAS: MVC + DRV/r (weeks 0–4)	15	0.69 (0.58, 0.76)	1.00	—
MIDAS: MVC + DRV/r (weeks 0–12)	15	0.69 (0.59, 0.73)	1.00	0.9349
A5160s arm A: EFV + LPV/r	21	0.61 (0.52, 0.68)	1.14	0.2651
A5160s arm B: LPV/r + 2NRTIs	22	0.53 (0.38, 0.66)	1.31	0.0063
A5160s arm C: EFV + 2NRTIs	25	0.63 (0.57, 0.70)	1.09	0.3909
A5166s arm C: EFV + 2NRTIs	16	0.67 (0.60, 0.73)	1.03	0.5986
Phase 2				
MIDAS: MVC + DRV/r (weeks 0–4)	15	0.021 (0.009, 0.039)	32.65	—
MIDAS: MVC + DRV/r (weeks 0–12)	15	0.025 (0.020, 0.029)	28.03	0.6529
A5160s arm A: EFV + LPV/r	21	0.045 (0.035, 0.048)	15.32	0.0024
A5160s arm B: LPV/r + 2NRTIs	22	0.046 (0.043, 0.049)	15.02	0.0005
A5160s arm C: EFV + 2NRTIs	25	0.036 (0.032, 0.042)	19.49	0.0176
A5166s arm C: EFV + 2NRTIs	16	0.055 (0.046, 0.070)	12.60	0.0001

* *P* values come from a Wilcoxon rank sum test not adjusted for multiple comparisons of differences in decay estimates between the MIDAS study and arms from 2 comparison studies; decay estimates are reported from A5160s and A5166s from models fit through week 8; a model fit through week 12 of the MIDAS data is also shown as a comparison to the model run through week 4.

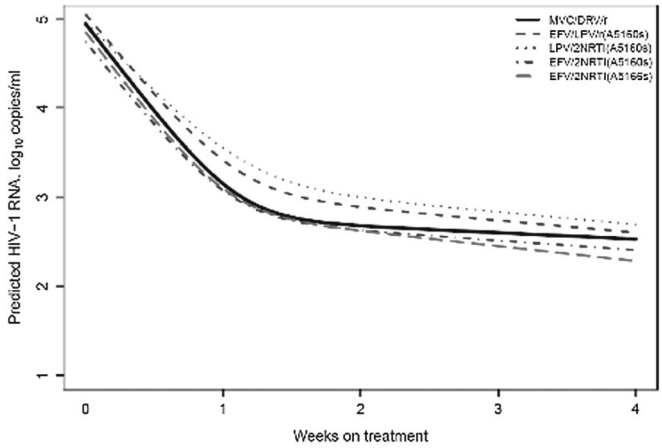

FIGURE 1. Biexponential VL decay curves in the MIDAS study and 2 different ACTG clinical trials with NRTI-sparing arms. Using primary data from 2 AIDS Clinical Trials Group studies: EFV plus LPV/r, LPV/r plus 2NRTIs, and EFV plus 2NRTIs in A5160s[28] and EFV plus 2NRTIs in A5166s.[29]

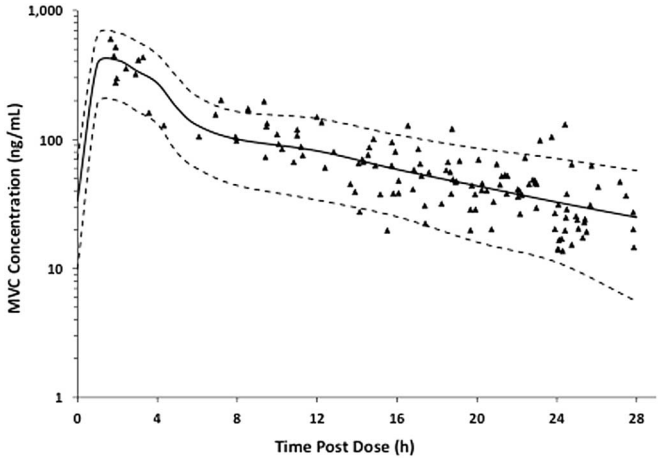

FIGURE 2. MVC concentration−time data in 24 subjects receiving 150 mg once daily with DRV/r 800/100 mg once daily. Solid line is the median simulated curve, and dashed lines represent the 95th percentile CI.

collected at week 8 in the current study, a sensitivity analysis was conducted to determine if observed decay rates were affected by fitting a model to week 4. We found no significant differences between the first- and second-phase decay rates of models run through week 4 or through week 12 ($P > 0.7$).

Median (Q_1, Q_3) transition time (the day and HIV RNA level at which production of HIV RNA decay from short- and long-lived cells is equal) was longer with MVC/DRV/r [13 days (11, 17)] compared with EFV plus LPV/r and EFV plus 2NRTIs in A5160s [12 days (11, 13)] and EFV plus 2NRTIs in A5166s [11 days (10, 13)]. An earlier median transition time was observed when compared with the LPV/r plus 2NRTIs arm [14 days (12, 19)]. Median predicted VL at transition was higher for MVC/DRV/r compared with the two EFV plus 2NRTIs arms (2.79 $\log_{10}$ copies per milliliter vs. 2.65 and 2.78). Median-predicted VL at transition was lower than EFV plus LPV/r and LPV/r plus 2NRTIs (2.93 and 2.95 $\log_{10}$ copies per milliliter, respectively).

Pharmacokinetics

A total of 145 MVC plasma concentration–time points were collected. Of these, 59 fell within the 20- to 28-hour C_{trough} collection window and 133 were used for modeling. From the raw data, the average peak (between 1 and 4 hours post dose) was 363 ng/mL and the average ± SD C_{trough} (between 20 and 28 hours post dose) was 39.3 ± 22.8 ng/mL. Overall, individual C_{trough} values ranged from 13.7 to 130 ng/mL (Q1, 23.4 ng/mL; Q3, 46.5 ng/mL). A linear 2-compartment model provided reasonable fits to the data (Fig. 2). The modeled MVC clearance (CL/F) was 48 ± 8.4 L/h. Central distribution volume (V_c/F), intercompartmental clearance (CL_d), and peripheral distribution volume (V_p/F) were 213 ± 35 L, 42.5 ± 21.6 L/h, and 278 ± 167 L, respectively. The median modeled AUC_{24} was 3073 ng·h/mL, and the steady-state concentration (C_{avg}) was 128 ng/mL. The population half-life ($T_{1/2}$) was estimated to be 10.3 ± 3.5 hours. The modeled MVC peak (C_{max} at 2 hours post dose) and C_{trough} (at 24 hours) concentrations were 415 and 36.1 ng/mL, respectively. VF was not explained by MVC plasma concentrations (Table 1).

DISCUSSION

The MIDAS study is the first to explore the virologic activity of the nucleos(t)ide-sparing regimen of MVC/DRV/r in treatment-naive patients. Twenty-one of the 24 treatment-naive participants (87.5%) treated with MVC/DRV/r 150/800/100 mg once daily in this study had VL <50 copies per milliliter at week 24. At 48 weeks, VL was <50 copies per milliliter in 22 of 24 participants (92%). Notably, both participants with VL >50 copies per milliliter at week 48 had pretreatment VL >100,000 copies per milliliter, but one of them (patient A in Table 1) achieved VL <50 copies per milliliter after almost 2 years on MVC/DRV/r. Virologic response to MVC/DRV/r was durable through week 96 with all but 2 participants (90%) maintaining viral suppression. CD4 counts increased by a median of 216 cells per cubic millimeter from baseline to week 96. The regimen was well tolerated.

Of the NRTI-sparing regimens investigated in treatment-naive patients to date, MVC 150 mg plus atazanavir/ritonavir 300/100 mg (MVC/ATV/r) has the closest antiretroviral drug composition to MVC/DRV/r. In study A4001078, 44 of 59 patients (74.6%) treated with MVC/ATV/r had VL <50 copies per milliliter at week 48,[30] dropping to (40/59) 67.8% at week 96.[30] The corresponding suppression rates for atazanavir/ritonavir 300/100 mg plus fixed-dose tenofovir/emtricitabine were 83.6% and 82.0%, respectively. Hyperbilirubinemia was more common with MVC/ATV/r. These results coupled with the relatively limited central nervous system penetration of atazanavir[31] have reduced enthusiasm for MVC/ATV/r. In the SPARTAN study, atazanavir 300 mg twice daily plus raltegravir 400 mg twice daily was associated with high rates of raltegravir resistance during VF and treatment-limiting hyperbilirubinemia.[3] Similarly, LPV/r 400/100 mg twice daily plus EFV 600 mg daily was associated with high rates of NNRTI resistance during VF.[1] We recently reported

that, among patients with pretreatment VL >100,000 copies per milliliter, DRV/r 800/100 mg once daily plus raltegravir 400 mg twice daily was associated with higher than expected rate of VF and a propensity for raltegravir resistance during VF.[4] LPV/r plus raltegravir was noninferior to LPV/r plus tenofovir/emtricitabine at week 96 (66.3% vs. 68.6%, respectively), but the mean baseline VL was relatively low (4.25 $\log_{10}$ copies per milliliter) in that study.[2] No 2-drug NRTI-sparing regimen is currently recommended, although DRV/r plus raltegravir is being investigated further (ANRS 143; NCT01066962).

The average MVC C_{trough} achieved with MVC/DRV/r 150/800/100 mg daily in MIDAS was 39.3 ng/mL. Although C_{trough} >25 ng/mL was associated with a higher probability of virologic response in MERIT,[20] it was not determinative of success in our study. The 2 participants (A and B) with C_{trough} measurements at VF had levels >25 ng/mL. Also, none of 3 participants who had C_{trough} <25 ng/mL at 50%–100% of assessed time points experienced VF (data not shown). The modeled MVC C_{avg} of 128 ng/mL in the current study exceeds the C_{avg} (75 ng/mL) associated with virologic response in MERIT. MVC C_{avg} may have a better prognostic measure of virologic response than the C_{trough}.[20] Overall, our PK results are consistent with other studies that investigated once-daily dosing of 150 mg MVC with DRV/r 800/100 mg.[22,32] MVC plasma exposures with the 150 mg once-daily dose in MIDAS were also similar to levels achieved with the approved 300 mg twice-daily dose when administered in the absence of potent CYP3A4 inhibitors and/or inducers.[33] Given potential differences in virologic suppression provided by DRV/r versus lamivudine/zidovudine, it is possible that MVC C_{trough} and C_{avg} that correlate with virologic success with MVC/DRV/r may differ from the levels identified in MERIT (MVC plus lamivudine/zidovudine), but our study was not designed to address this. All but 2 participants in our study had VL <50 copies per milliliter at week 48. All MVC concentrations were quantifiable, indicating that all subjects were taking MVC at the time of plasma sampling. The Department of Health and Human Services suggests a minimum trough concentration of 50 ng/mL in treatment-experienced patients with VF.[5]

By comparing virus decay during MVC/DRV/r treatment to previously reported decay rates with EFV- and LPV-containing regimens, we found that phase 1 decay (ie, virus decay in the first 10 days of treatment) with MVC/DRV/r was faster than LPV plus 2NRTIs and comparable to EFV plus 2NRTIs[28,29] and EFV plus LPV.[28] This is important because phase 1 virus decay rate, which reflects turnover of short-lived infected cells,[34] correlates with subsequent virologic response[35] and can inform which experimental regimens merit further evaluation.[28] EFV-containing regimens have demonstrated faster phase 1 decay than LPV plus 2NRTIs[28] and triple nucleoside antiretroviral therapy.[29] In contrast to phase 1 decay, phase 2 decay rate reflects turnover of long-lived infected cells.[34] In our model, phase 2 decay was slower with MVC/DRV/r than EFV- and LPV-containing regimens previously reported. One potential explanation for this is that antiretroviral agents that act before viral integration such as EFV and MVC may increase the proportion of infected cells with longer half-life and thereby lower the apparent rate of phase 2 decay.[28] Indeed, EFV has slower phase 2 decay than LPV, which acts after integration.[28] Overall, the virus decay pattern of MVC/DRV/r bears similarities with EFV-containing regimens, suggesting potent inhibition of infectious virion production.

Although the small number of participants and the single-arm design are limitations of our study, we have generated important virologic and PK data on MVC/DRV/r. Our ability to characterize emergent resistance during VF was limited by occurrence of very few VFs and the low level of viremia in most of those who did. Another limitation of our study is that few participants had advanced HIV infection (median CD4 count at entry was 455 cells per cubic millimeter and those with CD4 <100 cells per cubic millimeter were excluded). Therefore, our results may not apply to patients with very low CD4 counts. Finally, of the 4 participants with baseline VL >100,000 copies per milliliter in the study, 2 had VF at week 48 although one of them achieved viral suppression at week 84 on MVC/DRV/r. This is in contrast to a single VF among 20 subjects with VL <100,000 copies per milliliter at baseline. Although these are interesting observations, the small size of this study limits our ability to rigorously compare virologic responses in the different baseline VL strata. The small number of patients enrolled in this study and the variable blood sampling time limit the possibility to draw definitive conclusions on the potential association (or lack of association) between virologic outcome and MVC PKs.

In conclusion, results of the MIDAS study support further evaluation of MVC/DRV/r 150/800/100 mg once daily for initial treatment of R5 HIV-1. A large, multicenter, clinical trial (MODERN) is already underway (NCT01345630). MODERN and other future studies should determine the virologic efficacy of MVC/DRV/r across baseline VL strata and characterize the resistance consequences of VF in patients receiving MVC/DRV/r, the PK correlates of virologic success, and the impact of NRTI sparing on metabolic complications associated with HIV and contemporary antiretroviral therapy.

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